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ANNALS OF
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VOLUME 14 NOVEMBER, 1940 NUMBER 5

THE RÔLE OF GONADAL AND ADRENAL CORTICAL HORMONES IN THE PRODUCTION OF EDEMA * †

By GEORGE W. THORN, F.A.C.P., *Baltimore, Maryland,* and KENDALL EMERSON, JR., *New York, N. Y.*

FEMALE SEX HORMONES

THE occurrence of generalized edema, associated with menstruation has been reported by Thomas,[1] Sweeney,[2] Molnar and Gruber [3] and Atkinson and Ivy.[4] Experimentally it has been observed [5] that the intramuscular injection of large doses of crystalline sex hormones (estrone, estradiol, testosterone and progesterone) in both male and female dogs resulted in a striking, but temporary, retention of sodium, chloride and water. Qualitative as well as quantitative differences were also noted in the effect of treatment with sex hormones on the renal excretion of potassium, phosphate and nitrogen.[5]

In a recent study [6] it was noted that 24 of a group of 50 normal female subjects gained 1 kg. or more during the week immediately preceding menstruation. Shortly after the onset of menstruation (24 to 72 hours) a diuresis occurred and the subjects lost weight. Less frequently a transient gain in weight was noted at, or about, the expected time of ovulation. In a limited number of subjects it was possible to establish the approximate date of ovulation by determining the time at which pregnandiol, an excretion product of progesterone (corpus luteum), appeared in the urine.

In subjects in whom there was no dietary restriction (chart 1) it is possible that an increased ingestion of food was responsible in part for the total weight gain which occurred premenstrually.[6] However, carefully controlled balance studies in other subjects (chart 2) revealed that under constant dietary conditions, the premenstrual gain in weight was associated with a striking retention of sodium, chloride and water. The diuresis

* Read at the Cleveland Meeting of the American College of Physicians, April 3, 1940.

From the Chemical Division, Medical Clinic, The Johns Hopkins University and Hospital, Baltimore, Maryland.

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which followed the onset of menstruation was associated with an increased renal excretion of these electrolytes. Studies of the urinary excretion of female sex hormones during the same period indicated a fluctuation in the excretion of female sex hormones which could be correlated in most instances with the cyclical changes in the excretion of sodium, chloride and water. Studies in a control male subject during a period of 40 days revealed only slight fluctuations in the excretion of sodium, chloride and water (3 to 5 day cycle).

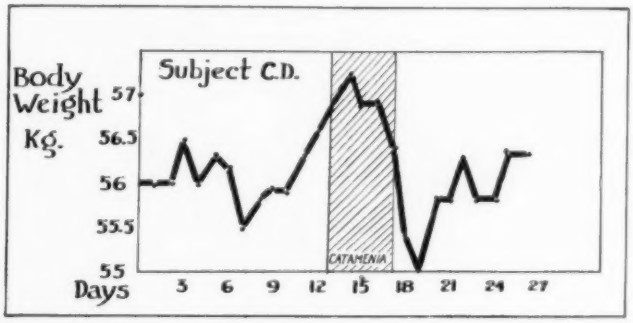

CHART 1. Changes in body weight during the menstrual cycle. Normal subject. Diet uncontrolled.

Patient E. K., a white, married female, 50 years of age, had had a supravaginal hysterectomy performed 11 years previously for uterine myomata. The ovaries had been left intact. Electrolyte balance studies * in this patient revealed a definite cyclical change in mineral excretion during a 24 day period (chart 3). This was associated with a cyclical change in sex hormone excretion. Ovulation and subsequent corpus luteum formation could not be established with certainty in this patient since it was impossible to perform endometrial biopsies. The absence of pregnandiol in the urine of this patient was also consistent with the observations of Venning and Browne on hysterectomized patients.[9]

Patient L. K., a white, married female, 36 years of age, had had a supravaginal hysterectomy and bilateral oöphorectomy performed 18 months previously. Electrolyte balance studies * revealed no significant fluctuation in the urinary excretion of electrolytes during a 30 day period. Furthermore, there appeared to be no significant change in sex hormone excretion during this period. However, the urine did contain a rather high titer of follicle-stimulating hormone. The absence of estrogenic hormone in the

* These patients were studied on the metabolism ward of The Johns Hopkins Hospital and were permitted to be up and about the ward under supervision. The diet and fluid intake were kept constant. The food was purchased in five day lots and an aliquot, representing one-half of one day's diet, was weighed, dried and analyzed. The diet was so selected that it approximated neutrality. Twenty-four hour urine specimens were collected, measured and preserved with toluene. Electrolyte determinations [6] and assays of estrogenic activity [7] were made on aliquots of three day pooled urine specimens. Pregnandiol was determined according to the method of Venning.[8]

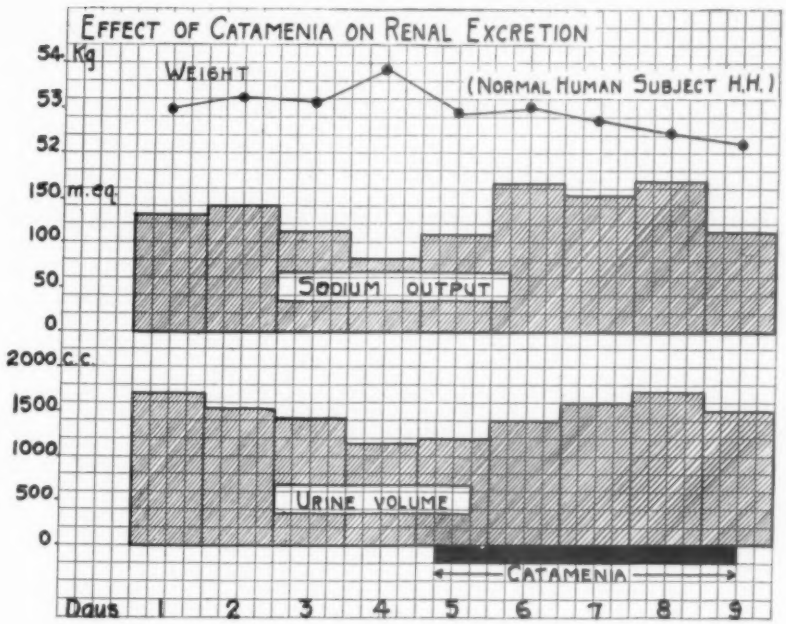

CHART 2. Premenstrual retention of sodium and water. Normal subject. Constant diet and fluid intake. (The daily intake of sodium was 122.4 m. eq.)

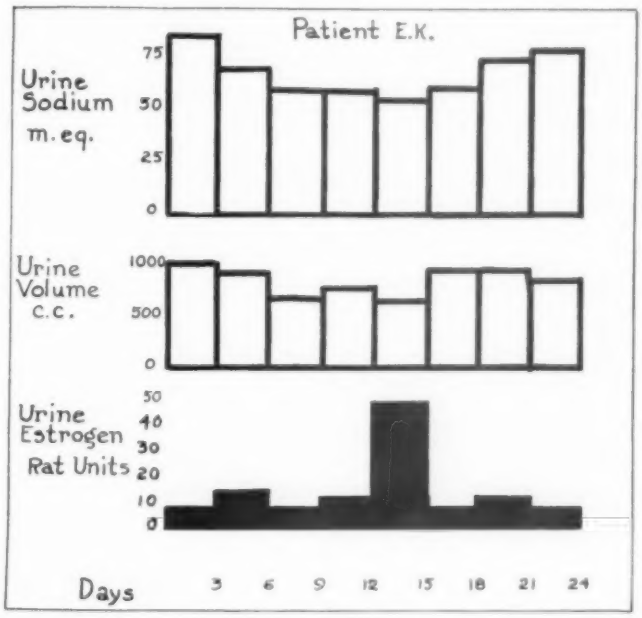

CHART 3. Cyclical change in urinary excretion of sodium, water and estrogen. Hysterectomized patient. Constant diet and fluid intake. (The daily intake of sodium was 78.0 m. eq.)

urine and the presence of follicle-stimulating hormone were compatible with the diagnosis of primary ovarian deficiency. It is particularly noteworthy that although this patient failed to show any cyclical retention of sodium and chloride at the time of this study, there had been a very definite history of episodes of pre-menstrual edema prior to the removal of the uterus and both ovaries.

The cyclical retention of significant quantities of sodium, chloride and water in patient E. L., hysterectomized, but with both ovaries intact, suggested that in normal subjects not all of the retention of sodium, chloride and water could be accounted for on the basis of local change in the size of the uterus.[10] Furthermore it appeared that the uterus was neither necessary nor responsible for the phenomenon of cyclical change in renal excretion of electrolytes during the menstrual cycle. The dependence of the phenomenon of cyclical retention of sodium, chloride and water on the presence of functioning ovarian tissue is indicated by the studies on patient L. K. following the removal of the uterus and both ovaries. This is further substantiated by the absence of marked cyclical changes in electrolyte excretion in a normal male control subject. Although these studies suggest that the ovarian hormones have a direct effect on the renal excretion of electrolytes, this fact has not been proved. It is entirely possible that the salt and water retaining-effect of sex hormones may be mediated in part or entirely through other glands of internal secretion.

Clinical Considerations

1. *Premenstrual "Tension."* Many patients noted puffiness of the eyelids, hands, feet or abdomen during the 48 hours immediately preceding the onset of menstruation. These signs were usually accompanied by headache and some degree of abdominal distention. In most instances symptoms were not severe and did not require treatment.

2. *Generalized Premenstrual Edema.* Fortunately the incidence of patients presenting signs and symptoms of generalized fluid retention during the premenstrual period was small. Great benefit was obtained by weight reduction when the patient's weight exceeded normal,* [11] by absolute restriction of sodium chloride in the diet during a 7 to 10 day period preceding the onset of menstruation and by the administration of supplementary potassium therapy. Potassium therapy greatly augmented the effectiveness of the low-sodium diet. Potassium citrate, 10 c.c. of a 20 per cent solution, was given in fruit juice, two or three times daily (total of 30 c.c. daily).

3. *Unexplained Gain in Weight During Treatment for Obesity.* Frequently during the course of treatment for obesity by means of a low caloric diet, female patients, much to their discouragement, either failed to lose weight or actually gained. A sudden gain in weight during the course of dietary restriction was not only discouraging to the patient but was also

* The method of Willoughby [11] for estimating ideal weight is recommended.

perplexing to her physician whose first reaction was to suspect dietary indiscretions.

In several patients it was observed that the gain in weight during a dietary regimen of low caloric intake was related to a temporary retention

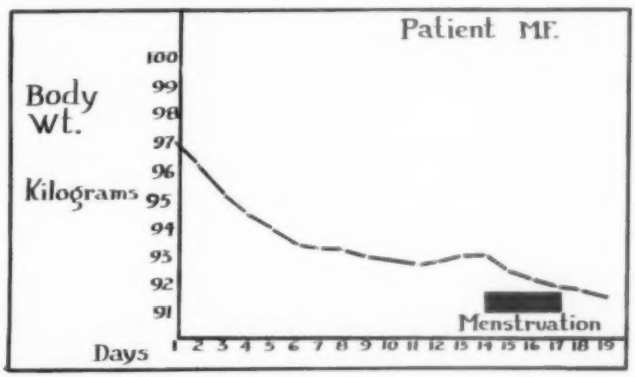

CHART 4. Premenstrual gain in weight during constant, low-calorie dietary regimen for treatment of obesity.

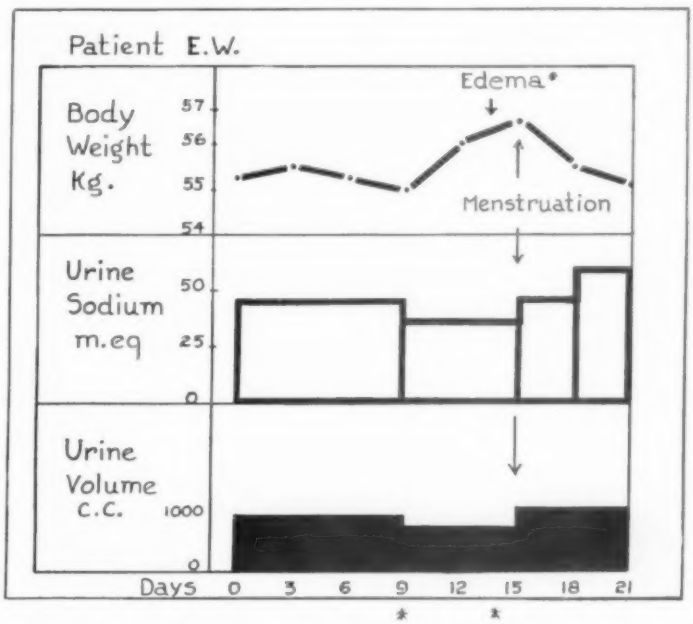

CHART 5. Premenstrual edema in patient with nephritis (constant diet). The daily intake of sodium was 44.4 m. eq.

of sodium, chloride and water during the premenstrual period (chart 4). Following the onset of menstruation a diuresis usually occurred and the patient lost weight. The ability to predict these episodes was of great aid in the care and treatment of obese female patients. Restriction of sodium

and chloride in the diet, supplemented by added potassium therapy (vide supra) aided greatly in reducing the retention of salt and water. Sufficient fluid was permitted to ensure a 24-hour urine volume of 1500 c.c. This form of therapy, however, was limited to a 4 to 7 day period preceding menstruation. With the onset of menstruation, all therapy with the exception of the low caloric diet, was discontinued immediately.

4. *Nephritis, Hepatic Cirrhosis with Ascites, Hypoproteinemia and Local Obstruction to Venous or Lymphatic Flow.* Female patients suffering from disorders which predispose to water retention may accumulate excessive quantities of extracellular fluid during the premenstrual period. The rapid appearance of edema in these patients at this time often suggests an exacerbation of the underlying disease.

A *B*

FIG. 1. *A* was taken on the ninth day of the study. *B* was taken on the fourteenth day of the study. (See chart 5.)

Patient D. W., a white, married female, 26 years of age, suffering from chronic glomerular nephritis, had noted that on several occasions a sudden, marked transient edema had appeared 24 to 48 hours preceding the onset of menstruation (figure 1). The appearance of edema was associated with a reduced urinary output and a striking gain in weight. Shortly after the onset of menstruation an increase in urine volume was noted, the edema rapidly disappeared and there was marked weight loss (chart 5). The rapid, spontaneous disappearance of the edema with the onset of menstruation made it appear unlikely that an exacerbation of the nephritis had occurred. Furthermore, no change was observed in the quantity of albumin or formed elements in the urine at that time.

The volume of ascitic fluid in patients with hepatic cirrhosis was observed to increase during the premenstrual period. With the onset of menstruation an appreciable reduction in ascites was noted. This was associated with a diuresis and loss in weight. Patients with a low concentration of serum protein and patients with obstruction to venous or lymphatic circulation were also observed to retain excessive quantities of sodium, chloride and water during the premenstrual period. Frequently the excessive retention of fluid at this time resulted in the appearance of edema. Following the onset of menstruation the edema disappeared rapidly.

In the treatment of edema in patients with nephritis, it is desirable to use a diet of alkaline ash in addition to a restricted sodium chloride intake. Added potassium therapy is contraindicated in these patients, as an increase in serum potassium frequently complicates the renal disease. In patients with edema, without demonstrable renal damage, the premenstrual retention of fluid may be greatly reduced by restricting the sodium chloride intake and by administering supplementary potassium medication during this period.

Male Sex Hormones

The striking and immediate gain in weight which follows testosterone propionate therapy in castrate male patients is well known. Experimental

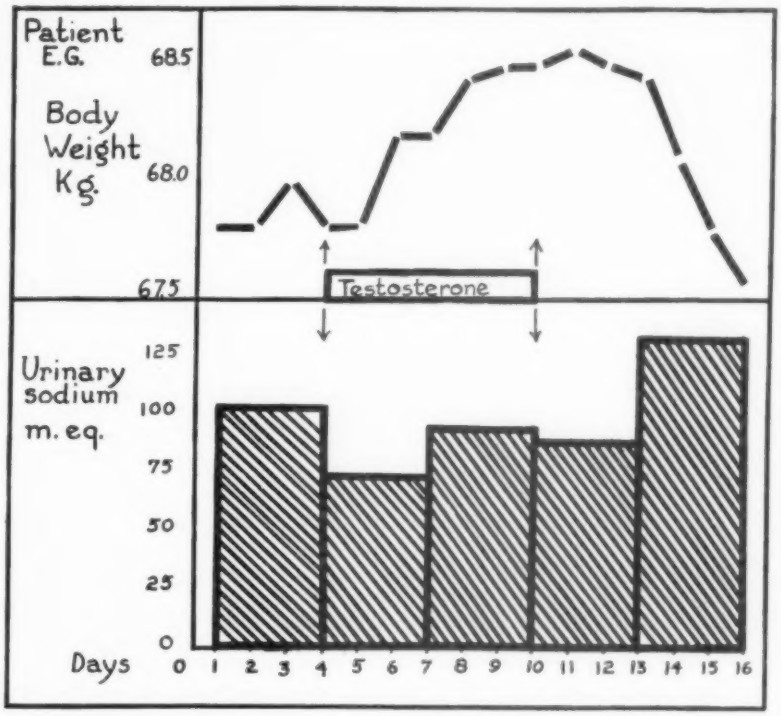

Chart 6. Retention of sodium during testosterone therapy. Constant diet. The daily intake of sodium was 100.0 m. eq.

studies in dogs [5] indicated that although testosterone treatment was associated with a striking retention of nitrogen, phosphorus and potassium, appreciable quantities of sodium, chloride and water were also retained, particularly during the initial period of treatment. Similar observations were made on a male subject following testosterone propionate therapy (chart 6). In this patient, treatment was followed by a striking retention of sodium, chloride and water, associated with a rapid gain in weight. Withdrawal of treatment was followed within 48 hours by an increase in the renal excretion of sodium, chloride and water with a corresponding loss in body weight. The recent studies of Kenyon, et al.[12] indicate that a large part of the initial weight gain in eunuchs treated with testosterone can be accounted for on the basis of sodium, chloride and water retention. Since testosterone propionate is not strikingly potent in its "sodium-retaining effect" [5] excessive salt and water retention is not a frequent complication of clinical treatment with this hormone.

Adrenal Cortical Hormones

Recent studies indicate a close chemical relationship between the sex hormones, particularly progesterone, and certain adrenal cortical hormones, particularly desoxycorticosterone.[13] As might be anticipated, there is some overlapping in the physiological action of the two groups of compounds.

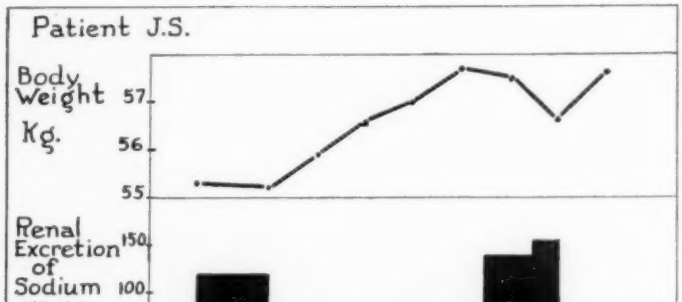

Chart 7. Effect of desoxycorticosterone acetate treatment on body weight and renal excretion of sodium. Addison's disease. Constant diet. (The daily intake of sodium was 80.4 m. eq.)

Thus it has been observed that treatment with progesterone greatly increased the period of survival of bilaterally adrenalectomized animals.[14] Furthermore the similarity in the clinical picture produced by certain tumors of the adrenal cortex and by arrhenoblastomata of the ovary is well known.

The rôle which the adrenal cortex plays in the regulation of electrolyte balance is of great importance.[15] It has been demonstrated that treatment with adrenal cortical extract resulted in a striking retention of sodium, chloride and water in patients with Addison's disease as well as in normal subjects.[16] In the past, however, edema has been an infrequent complication of adrenal extract therapy since the costliness of extract necessarily limited the quantity of hormone which could be administered. The synthesis of desoxycorticosterone acetate, however, has made available a very potent adrenal cortical hormone preparation at a cost which most patients can afford.

Treatment with desoxycorticosterone acetate resulted in a striking retention of sodium, chloride and water in patients with Addison's disease (chart 7).[17, 18] Treatment with synthetic hormone was associated on occasions with the retention of excessive quantities of salt and water with the appearance of edema.[18] This complication occurred most frequently when supplementary sodium chloride therapy was given. Great care must be exercised in the administration of desoxycorticosterone acetate therapy if excessive salt and water retention is to be avoided. Restriction of sodium chloride intake and supplementary potassium medication (vide supra) are effective measures in preventing or reducing edema resulting from desoxycorticosterone acetate therapy.

A striking retention of sodium and chloride was observed in a group of five normal subjects during treatment with daily intramuscular injections of 10 to 15 mg. of Percorten * (Ciba, desoxycorticosterone acetate in sesame oil) (table 1 and chart 8). The subjects were maintained on a constant diet supplemented with 9 gm. of added sodium chloride. During a period of four days of treatment an average weight gain of approximately 1.5 kg. was observed. The retention of sodium and chloride during this period was accompanied by an increased excretion of potassium. Blood studies revealed a slight increase in the serum concentration of sodium and chloride despite hemodilution. No significant change in blood pressure was observed during the short period of hormone therapy. Slight puffiness of the face and ankles was observed in two of the normal subjects on the fourth day of treatment. Withdrawal of hormone therapy was followed by a marked excretion of sodium, chloride and water, weight loss, retention of potassium, hemoconcentration, a decrease in the serum concentration of sodium and chloride and a significant increase in serum potassium.

The increased sodium, chloride and water retention which occurred in normal subjects during the period of treatment with desoxycorticosterone acetate is of interest in relation to the studies of Anderson et al.[19] These investigators have reported electrolyte changes in patients with hyperfunction

* The Percorten, desoxycorticosterone acetate in sesame oil, used in this study was provided through the courtesy of Dr. E. Oppenheimer, Ciba Pharmaceutical Products, Inc., Summit, N. J.

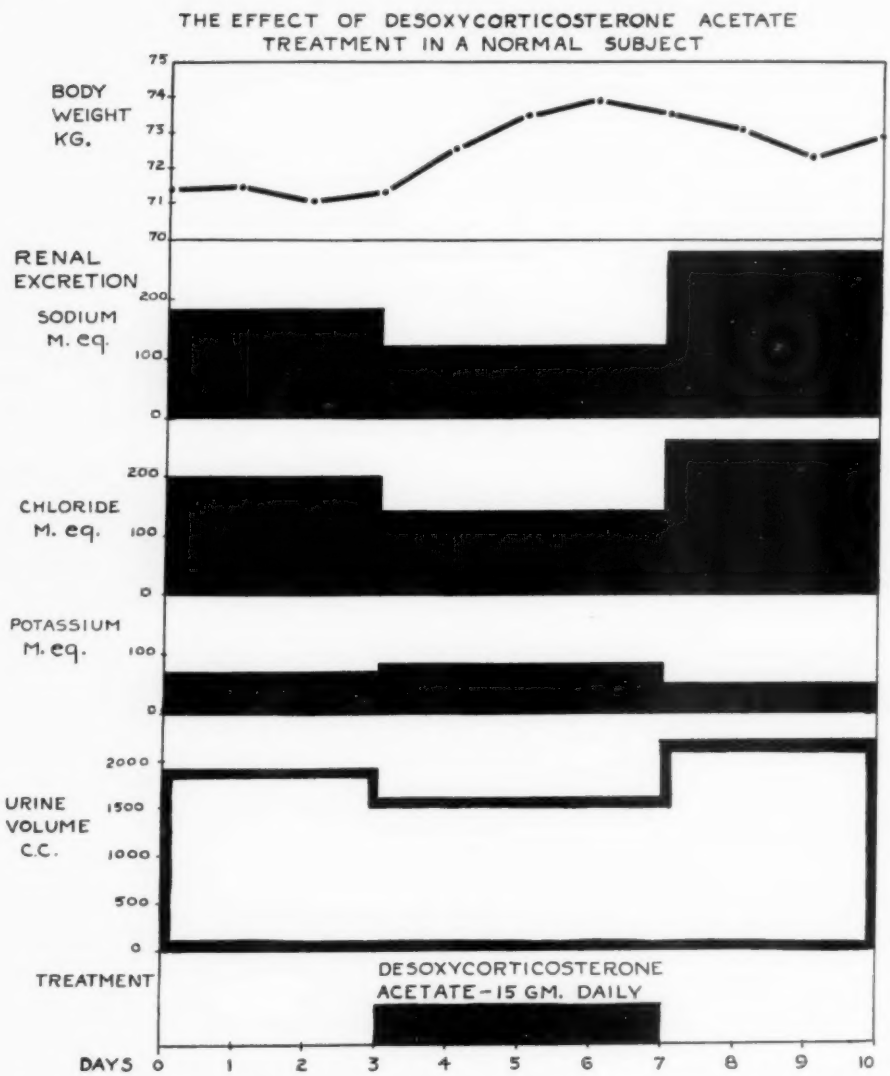

CHART 8. The effect of desoxycorticosterone acetate treatment on body weight and renal excretion of electrolytes (normal subject). The constant diet contained 192.1 m. eq. of sodium, 203.5 m. eq. of chloride and 84.0 m. eq. of potassium.

of the adrenal cortex which were the antithesis of those observed in patients with Addison's disease.

DISCUSSION

It cannot be stated from clinical studies which of the female sex hormones plays the more important rôle in regulating electrolyte balance. Certainly, the retention of electrolytes during the premenstrual period is much more striking than that which is observed at the time of ovulation. This

TABLE I

The Effect of Desoxycorticosterone Acetate Treatment on the Renal Excretion and Serum Concentration of Electrolytes in Normal Subjects

Average daily value for 5 normal subjects	March 17–20 Control	March 20–24 Treatment	March 24–27 Control
Urinary Studies			
Urine volume c.c.	1468	1200	1591
Urinary sodium m.eq.	175.2	94.0	244.8
Urinary chloride m.eq.	184.6	122.6	240.4
Urinary potassium m.eq.	65.8	80.5	43.3
Urinary inorganic phosphorus gm.	.834	.875	.880
Urinary ammonia nitrogen gm.	.533	.641	.636
Blood Studies			
Serum sodium m.eq. per liter	139.1	141.9	139.4
Serum chloride m.eq. per liter	100.5	106.1	95.8
Serum potassium m.eq. per liter	4.9	5.2	6.3
Serum carbon dioxide combining power m.eq. per liter	28.5	29.3	28.5
Blood non-protein nitrogen mg. per 100 c.c.	35	33	34
Blood sugar mg. per 100 c.c.	93	88	91
Total serum protein gm. per 100 c.c.	7.11	6.61	6.64
Hematocrit: per cent volume of packed cells	46.2	43.3	46.2

suggests the possibility that progesterone, or progesterone in addition to estrogens, is more effective than the estrogens alone. In experimental studies [5] it has been demonstrated that the effect of progesterone on electrolyte balance resembles more closely the effect of adrenal cortical hormone than either estrone or testosterone. Furthermore, the increased survival period of adrenalectomized animals treated with progesterone,[14] suggests that progesterone has a significant sodium and chloride-retaining effect, since prolongation of the survival period of these animals parallels closely the ability to maintain electrolyte balance.

It appears unlikely that an increase-over-normal in the secretion of sex hormones is the factor responsible for the premenstrual edema noted in these patients. The absence of edema in most normal patients, and the greatly increased retention of electrolytes which was observed in patients suffering from complications which favored the accumulation of excessive quantities of fluid, suggest that premenstrual edema is probably the result of normal cyclical changes in sex hormone secretion acting as a precipitating factor in

patients with some underlying change which predisposes to excessive retention of sodium, chloride and water.

Summary

In normal women cyclical changes in female sex hormone excretion were observed to be associated with striking changes in the excretion of sodium, chloride and water. Similar changes were also observed in a patient who had been hysterectomized several years previously. In a patient who had had both ovaries and uterus removed 18 months previous to this study no cyclical change in sex hormone excretion or electrolyte balance was noted during a period of 30 days.

In obese patients a transient gain in weight was occasionally observed during a weight-reducing regimen. In some instances, the gain in weight could be accounted for by a premenstrual retention of sodium, chloride and water. A retention of sodium, chloride and water also occurred during the premenstrual period of patients suffering from disorders which predisposed to fluid accumulation such as nephritis, cirrhosis of the liver with ascites, hypoproteinemia, and obstruction to venous or lymphatic circulation. Unless fully appreciated, the premenstrual retention of fluid in these patients could be mistaken for an exacerbation of the underlying disease.

Although retention of an appreciable quantity of sodium, chloride and water occurred during the initial period of testosterone propionate therapy, edema was neither a frequent nor striking complication of male sex hormone therapy.

Desoxycorticosterone acetate therapy has a very striking sodium, chloride and water-retaining effect in normal subjects as well as in patients with Addison's disease. Great care must be exercised in the use of this hormone clinically, if excessive retention of these electrolytes is to be avoided.

Sodium chloride restriction and supplementary potassium medication were effective in moderating the sodium, chloride and water-retaining effect of both gonadal and adrenal cortical hormones.

Conclusions

The electrolyte balance of the body appears to be affected significantly by the steroid hormones of the gonads and adrenal cortex. Under certain conditions, these hormones may act as precipitating factors in the production of edema. Careful restriction of sodium chloride intake combined with supplementary potassium medication provides effective therapy in preventing or ameliorating the edema. Such therapy should not be used indiscriminantly.

The authors are indebted to Miss Mildred Caldwell, Supervisor of the Metabolism Ward, Miss Elizabeth Olsen, Dietician-in-Charge of the Metabolism Ward, Mr. Howard F. Conn and Drs. Daniel Kuhlmann and R. Palmer Howard for their continued assistance and coöperation.

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DILANTIN SODIUM: ITS INFLUENCE ON CONDUCT AND ON PSYCHOMETRIC RATINGS OF INSTITUTIONALIZED EPILEPTICS *

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REPORTS on the effectiveness of sodium diphenyl hydantoinate (dilantin sodium) in epilepsy have accumulated rapidly since Merritt and Putnam [1] inaugurated the use of the drug in 1938. Naturally most interest has devolved upon its use in the control of convulsions and upon its toxic effects—rash, anorexia, nausea, vomiting, ataxia, gingivitis,[2] and to a less extent delusions, hallucinations, prolonged confusion, agitation, depression, irritability, and suspiciousness.[3, 4] The toxic effects apparently are manifested earlier, more frequently, and more severely in patients over 40 years of age, and consequently the drug would seem to be of less danger in younger and better preserved individuals.[5]

In consonance with the alleviation of seizures almost all reports on dilantin sodium remark on the improvement in behavior, well-being, cooperation, alertness, general attitude, irritability, temperament, and personality of many patients.[3, 4, 6, 7, 8, 9]

We have been particularly interested in the effects of the drug on conduct, as well as on any change that might be reflected in intelligence and performance tests. For this study we have used 73 patients at the Caro State Hospital for Epileptics who have received dilantin sodium over a period of 12 to 18 months. The dosage ranged from 0.1 gm. (gr. 1½) to 0.5 gm. (gr. 7½) daily, depending upon anticonvulsant effects. The vast majority of patients were between 17 and 30 years of age, the youngest being 11 and the oldest 51 years. By "conduct" we included behavior, irritability, alertness, initiative, interest, general attitude, and coöperation, taking the sum total of these factors as determining the effect of the drug. The 1937 Revised Stanford-Binet was used for the determination of the intelligence quotient, and Grace Arthur's Point Scale of Performance Test for the performance quotient. On 55 of the subjects the intelligence quotient was compared with that obtained prior to the use of dilantin sodium, and on 25 the performance quotient was so compared.

Using the classification of the epilepsies adopted by the National Association for the Study of Epilepsy, we divided the patients into the following groups: 29 with idiopathic epilepsy; 25 whose epilepsy is a manifestation of cerebral agenesis; 12 whose convulsions reflect a previous meningo-encephalitis; and 7 whose epilepsy is ascribed to cerebral trauma.

Our results are summarized in the accompanying table.

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From the Caro State Hospital for Epileptics, R. L. Dixon, M.D., Superintendent.

TABLE I

	Idiopathic	Agenesis	Encephalitis	Trauma
Number of patients	29	25	12	7
Monthly seizure average of group before medication	510	666	398	215
Monthly seizure average of group during medication	87	153	154	42
Seizures decreased 75% or more	20	15	5	6
Seizures decreased 50%–75%	5	4	5	0
Seizures decreased 25%–50%	2	5	0	0
Seizures unimproved or increased	2	1	2	1
Conduct improved	14	9	3	3
Conduct unchanged	14	15	7	4
Conduct worsened	1	1	2	0
Rechecks 1937 Revised Binet	26	17	7	5
I.Q. raised over 10 points	6	1	1	0
I.Q. decreased over 10 points	4	0	1	0
Rechecks Grace Arthur	13	5	4	3
P.Q. raised over 10 points	4	1	3	1
P.Q. decreased over 10 points	1	2	0	0

The most striking feature is that in over 65 per cent of the patients the seizure incidence was reduced 75 per cent or more. The least reduction occurred in the encephalitic group, whereas the greatest was in the small traumatic group.

In a little less than one-half of the patients there was improvement in conduct. Here again the encephalitic group was less responsive than the others. One patient with idiopathic epilepsy, whose seizures were almost totally controlled, exhibited remarkable improvement in behavior, interest, and coöperation. Dilantin was withdrawn and, though he has had no recurrence of convulsions, he has returned to his former vituperative, surly, resistive manner. In another idiopathic epileptic, whose convulsions were quite well controlled by the drug, there was a repetitious occurrence of disturbed periods marked by paranoid ideas, auditory hallucinations, assaultiveness, and general battering-ram tactics. When dilantin was discontinued he again became the rather ingratiating, docile person he had been before the drug was administered, despite a sharp increase in the number of convulsions. In three patients the conduct change consisted of increased irritability, querulousness, and suspiciousness. Seizures had been considerably reduced in two of these boys, and increased a few in the other.

The comparison of psychometric results before and after dilantin administration was interesting. Although in comparing test results a variation of over 5 points is considered significant, we have selected a range of 10 points as being more indicative of a worthwhile variation between the former and latter determinations. The intelligence quotient was raised over 10 points in six idiopathic epileptics and reduced over 10 points in four others. All but one of these 10 individuals had a pronounced diminution in seizure incidence. One each of the agenesis group and of the encephalitic group likewise raised their intelligence quotients consonantal to a marked reduction in seizures. The improvement in intelligence rating was not confined to any

particular field—in some patients greatest improvement was shown in memory, in others reasoning and planning, in still others recognition of verbal absurdities.

On the Grace Arthur Performance Scale nine patients raised their quotients over 10 points, three of them from 30 to 44 points, while three reduced theirs. Eleven of the 12 had experienced a marked reduction in seizures; the twelfth had only a slight drop but scored a rise of 44 points in performance quotient. The improvement was mainly manifested by quicker perception, better planning, and speedier execution of the tests.

Discussion

In evaluating the effects of any medicinal agent in the treatment of institutionalized epileptics, certain intangible factors must be considered. Suggestion plays a rôle, but we believe we have extended the trial period long enough (12 to 18 months) to eliminate this factor. Environment must be taken into consideration, for most epileptics living in overcrowded institutional quarters and with the average mentality of such intramural patients, are irritable, explosive, and easily disquieted under certain circumstances. One or two uncoöperative, aggressive individuals can upset an entire group. Perhaps more of our patients would have shown improvement in conduct had they been in an environment free of overcrowding, tension, restlessness, and distraction. Nevertheless, they had all been in the institution long enough to have become adjusted to their surroundings and the attendant disturbances. We believe, therefore, that in this study too great weight need not be placed upon the effect of environment. Another possibility is that the improvement was spontaneous since we know that sometimes for no apparent reason some epileptics will gradually have fewer and fewer seizures and maintain a stationary level of deportment and intellectual activity. Our study group is too large to suggest that most of the improvement could be so explained.

Undoubtedly much of the betterment in conduct was due to the pronounced reduction in the number of seizures, giving these patients a greater feeling of security, lessening the hazards of attacks, and producing a sense of well-being and possibly elation. While this may be so, there were just about as many instances where a similar reduction of attacks was obtained in essentially the same types of individuals without producing an appreciable change in conduct. We have no explanation for this discrepancy.

One might expect that with the heightening of interest, initiative, and alertness shown by many of the patients, their intelligence ratings would be raised. They actually give the impression of being more intelligent than at the beginning of treatment. However, this appearance is deceptive for there obtained practically a balance between raised and lowered intelligence ratings in the face of equivalent seizure reduction. These results agree essentially with those reported by Fetterman [4] who found that dilantin showed no un-

favorable influence on intelligence or learning ability, and remarked that the intelligence ratings in his group of cases have been as good as, if not slightly better than, tests made in previous years.

Perhaps a little more weight can be attached to the raising of the performance quotient in nine patients while it was lowered in only three in spite of the fact that seizures were reduced in all of them. Probably the effect of the drug in lessening seizures, promoting confidence, a feeling of well-being, alertness, and initiative " removed the brakes," so to speak, from the patient's latent performance ability and gave a truer index of his capacity.

Summary and Conclusions

Twenty-nine chronic idiopathic epileptics and 44 patients with symptomatic epilepsy who have received dilantin sodium over a period of 12 to 18 months were observed from the standpoint of the drug's value in controlling seizures, its influence on conduct, its effect on psychometric ratings, and its relative value in the different groups of epilepsy.

1. About 65 per cent had a very marked reduction of seizure incidence.
2. About 50 per cent showed an improvement in conduct. This occurred in patients who had a pronounced diminution in the number of seizures, but as many showed no such improvement despite an equal reduction of attacks. We do not attempt to explain this fact.
3. There was no significant influence on intelligence ratings.
4. Performance ratings were raised appreciably in a small percentage of patients. The drug seemed to have a greater beneficial effect in this capacity than on intelligence.
5. There did not appear to be a definitely greater responsiveness to the drug by one group of epileptics over another.

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THE BLOOD SEDIMENTATION TEST AS A ROUTINE DIAGNOSTIC PROCEDURE; A CLINICAL EVALUATION OF 2063 CASES *

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The blood sedimentation test, one of the oldest and simplest of the laboratory procedures, was reëstablished as a test for pregnancy by Fåhraeus [1] in 1918. Although the specificity of the test for pregnancy was soon disproved, the procedure has received much attention since that time. In this country it has been used most frequently as a special rather than as a routine procedure.

The larger portion of the literature dealing with the sedimentation test has been concerned with the factors influencing the rate, the various methods of determination, and the results obtained from the use of the test in certain diseases. Few authors have recorded observations based upon the routine use of the test. Cutler [2] reported his experience with the sedimentation test based upon the study of 5,000 cases observed in hospital, dispensary, and office practice. Schattenberg [3] used the sedimentation test as a routine procedure in 1,100 cases consisting of applicants for health cards in the Dallas City Health Department, and patients in the outpatient dispensary of Baylor University. Gallagher [4] performed the test routinely in 685 cases as a part of the yearly health examination of preparatory school students. Wintrobe [5] used the test as a routine procedure in 767 cases in the diagnostic clinic of the Johns Hopkins Hospital. These authors agreed that the routine blood sedimentation test was of value. Other authors have stressed the value of the sedimentation test as a routine procedure, but without supporting evidence.

Material and Methods

Material. The present study is based upon a survey of the records of 2,063 patients observed in the Diagnostic Hospital of the New England Medical Center. The blood sedimentation test was performed as a routine procedure. The purpose of this study is an evaluation of the test in these cases. The patients were all hospital cases and represented all types of disease. As shown in table 1, the group was composed largely of adults, and only cases which had been completely studied were included.

Methods. The blood sedimentation tests were performed by a modification of the Westergren method,[6] which differed from the original only in that 5 per cent sodium citrate solution was used as the anticoagulant. Throughout the study the rate for a given patient was the routine admission

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From the Joseph H. Pratt Diagnostic Hospital.

rate, determined on blood obtained on the first morning of hospitalization, the patient having been without food for at least eight hours. The test was begun within 30 minutes of the time of the collection of the blood. The

TABLE I

Age and Sex Distribution of Cases

Age	Male	Female	Total
1–10	8	4	12
11–20	92	119	211
21–30	124	176	300
31–40	153	202	355
41–50	196	233	429
51–60	217	183	400
61–70	156	125	281
71+	44	31	75
Totals	990	1073	2063
	48%	52%	

tube was not allowed to vary from the exact vertical position; the rack stood at room temperature; and the rate was determined at the end of 20 minutes, one hour, and two hours.

In this study the one hour determination was considered to be the significant value. The 20 minute figure was helpful in discovering certain technical errors, leaking and clotting. The two hour determination was useful as a check on the one hour figure. Except in cases showing a very rapid rate, the sedimentation at the end of one hour represented from 40 to 60 per cent of the value at the end of two hours. In a few cases the one hour level amounted to 20 per cent or less of the two hour figure. In these cases, a repetition of the test gave the more usual relationship.

Normal Values. There is no complete agreement as to the normal sedimentation rate, even by the same method of determination. Westergren [6] in 1921 expressed the opinion that a rate of 10 millimeters in an hour was definitely pathological. In our series a sedimentation rate of more than 20 millimeters in one hour has been considered abnormal. The selection of this value was based upon a consideration of the literature and the experience of those who studied these individual cases. It corresponds independently to the value advocated by Bannick et al.[8] Arbitrarily, the cases were divided into the following groups.

Group I. Normal Sedimentation Rate—rates from zero to 15 millimeters at the end of one hour.

Group II. Borderline Sedimentation Rate—rates from 16 to 20 millimeters at the end of one hour.

Group III. Slightly Elevated Sedimentation Rate—rates from 21 to 30 millimeters at the end of one hour.

Group IV. Definitely Elevated Sedimentation Rate—rates greater than 30 millimeters at the end of one hour.

Table 2 shows the distribution of the sedimentation rates.

TABLE II

Distribution of the Sedimentation Rates

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0–15	16–20	21–30	31+		
Male	560 56.6%	76 7.6%	99 10%	255 25.8%	990	354 35.8%
Female	611 57.0%	114 10.6%	124 11.5%	224 20.9%	1073	348 32.4%
Totals	1171 56.7%	190 9.2%	223 10.8%	479 23.3%	2063	702 34.1%

DISCUSSION OF RESULTS

Results. Blood counts, urinalyses, and serological tests for syphilis are widely employed as routine diagnostic procedures. The purpose of this study is to indicate that the blood sedimentation test is important enough to be similarly employed even though it is non-specific.

In this series there were 176 cases, 8.5 per cent, showing changes in the serologic reactions of the blood, Wassermann, Hinton and Kahn tests having been performed. Similarly, there were 331 cases, 16 per cent, showing an abnormal blood count which gave specific information leading to the detection of the particular disease. Also, 207 cases, 10 per cent, were found to have some disease in which the urinalysis had given specific information leading to a diagnosis. Therefore, in 34.5 per cent of our cases the generally employed routine diagnostic tests were of specific value. On the other hand, a total of 702 cases, 34.1 per cent, showed an increased sedimentation rate, which, though not specifically, yet definitely indicated the presence of disease. However, these cases must be further analyzed to determine more accurately the value of the information obtained by the use of the sedimentation test as a routine diagnostic procedure.

Relationship of the Sedimentation Rate to the Diagnosis. The cases were divided into a group presenting no evidence of an organic disease, which may be considered as "negative"; and a group showing definite evidence of disease, which may be considered as "positive." This division was based upon the discharge diagnosis as recorded on the case record, grouped according to the "Standard Classified Nomenclature of Disease."[9] There was no doubt in the minds of the observers as to the absence of evidence of organic disease in the "negative" group. Insignificant organic disease,

however, was present in some portion of the cases classified as "positive." Table 3 shows the distribution of the cases according to these groups, and the sedimentation rates in each group.

TABLE III

Distribution of the Sedimentation Rates in Relation to Diagnosis

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0–15	16–20	21–30	31+		
Diagnosis "Positive"						
Male	380 47.5%	67 8.3%	98 12.3%	255 31.9%	800	353 44.2%
Female	330 44.1%	91 13.6%	109 14.7%	219 27.6%	749	328 42.3%
Totals	710 45.9%	158 10.2%	207 13.3%	474 30.6%	1549	681 43.9%
Diagnosis "Negative"						
Male	180 94.8%	9 4.7%	1 0.5%	0	190	1 0.5%
Female	281 86.7%	23 7.0%	15 4.8%	5 1.5%	324	20 6.3%
Totals	461 89.7%	32 6.2%	16 3.1%	5 0.9%	514	21 4.0%

Significance of an Elevated Sedimentation Rate in Diagnosis. In the group of cases in which no evidence of organic disease was discovered, there were five cases in which the sedimentation rate was more than 30 millimeters in one hour, and 16 cases in which it was between 21 and 30 millimeters. In Cutler's series[2] of 177 cases with an elevated rate, only eight cases showed no disease (4.5 per cent). Wintrobe[5] also mentioned that there were 31 of 136 cases (22.7 per cent) in which increased sedimentation rates were present, and were not adequately explained by the findings on examination of the patient. However, many of his patients were seen on only one occasion. Gallagher[4] reported five cases among 685 (0.7 per cent) in which there was an unexplained, slightly accelerated rate. Schattenberg,[3] on the other hand, found that some disease process was the cause for every accelerated sedimentation rate.

The records of these 21 patients without evidence of organic disease but with an increased sedimentation rate were subjected to a more careful study. The most striking fact was the presence of only one male in the group. He was found to have a sedimentation rate of 23 millimeters in one hour, and was discharged as a case of unclassified psychosis. However, he gave a

history of having been treated in a tuberculosis sanatorium for 18 months a few years before. While examination of the chest and of the sputum was negative, it is conceivable that tuberculosis may have accounted for the rapid sedimentation rate.

Of the five cases with a definitely elevated rate (over 30 millimeters in one hour) three were discharged as cases of simple obesity; two were discharged with the diagnosis of psychoneurosis. One of the patients with a diagnosis of psychoneurosis on discharge gave a history of painful swellings of the shoulder, arm, and hand, which had disappeared shortly before admission. The other patient was apparently normal except for what was thought to be a benign essential hypertension.

Of the 15 women with slightly elevated sedimentation rates, nine were discharged with a diagnosis of obesity, five as psychoneuroses and one with no evidence of disease. Of the cases of obesity, one gave a history of a subsiding thrombophlebitis on admission, and another was subsequently found to have been eight weeks' pregnant at the time of study. Of the five discharged as psychoneuroses, one showed diverticula of the colon, another had mild hypochromic microcytic anemia, and a third had a mild synovitis of the right wrist. The fourth patient had undergone extensive dental extractions a few weeks before admission, and the fifth had a fracture of the tibia, which had been reduced two weeks before admission. The patient discharged without evidence of disease was recovering from a severe infection of the upper respiratory tract at the time of admission.

Therefore, of the 21 cases with increased sedimentation rates, but without evidence of disease, detailed study of the records raised some doubt as to the absolute lack of explanation in 11 cases. The other 10 were considered to be cases of simple obesity. There is no apparent association of obesity and increased sedimentation rate, but the coincidence is noted.

Relationship of the Actual Sedimentation Rate to the Expected Rate. Certain organic diseases seldom produce an increase in the blood sedimentation rate. Other diseases, usually found to have an increase in the sedimentation rate, may be present in a given case without acceleration of the sedimentation rate. For example, a patient with rheumatic heart disease, but without evidence of rheumatic activity, would be considered to have a disease in which the sedimentation rate would be expected to be normal. For practical purposes, such a diagnosis might be considered a negative diagnosis in so far as the sedimentation rate was concerned.

Accordingly, the group of 1549 cases previously designated as having shown evidence of organic disease was subdivided into a group in which evidence of a disease usually associated with an increased sedimentation rate was discovered, and a group in which evidence of such a disease was lacking. The general table, as compiled by Cutler,[2] and modified by Bannick,[10] was used as a basis for this division. Consideration was also given to the findings of other authors, who studied the sedimentation rate in specific diseases. In general, accelerated rates were expected in chronic and

acute infections, malignancy, localized suppurations, and tuberculosis. Normal sedimentation rates were expected in simple catarrhal inflammations, chronic ulcerations, metabolic diseases, chronic valvular disease of the heart and allergic diseases. Table 4 shows the result of this division, and the relationship of the blood sedimentation rates to each of these groups.

TABLE IV

Relationship of the Expected Sedimentation Rate to the Actual Rate

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0–15	16–20	21–30	31+		
Normal Sedimentation Rate Expected						
Male	293 81.6%	35 9.7%	27 7.5%	4 1.2%	359	31 8.7%
Female	278 73.1%	48 12.6%	42 11.0%	12 3.3%	380	54 14.3%
Totals	571 77.2%	83 11.2%	69 9.3%	16 2.3%	739	85 11.6%
Increased Sedimentation Rate Expected						
Male	87 19.7%	32 7.2%	71 16.1%	251 57.0%	441	322 73.1%
Female	52 14.1%	43 11.7%	67 18.1%	207 56.1%	369	274 74.2%
Totals	139 17.1%	75 9.4%	138 17.0%	458 56.5%	810	596 73.5%

There is general agreement that a normal sedimentation rate does not rule out disease. In our series 868 cases, 56.1 per cent of the 1549 cases with evidence of an organic disease, showed a normal sedimentation rate. Even in the group of 810 cases with evidence of an organic disease usually associated with an increased sedimentation rate, 214 cases, 26.5 per cent, showed a normal rate. These findings are not entirely in agreement with other reports in the literature. Hirsh,[11] in a series of 205 determinations in cases in which the blood sedimentation rate was expected to be elevated, reported that every case showed an elevated rate. Wintrobe [12] expressed the opinion that normal rate was rarely found in the presence of organic disease. In 444 cases in which the corrected sedimentation rate was normal, manifest organic disease was found in only eight instances (1.8 per cent). However, he mentioned high values in a number of cases of infection in which a slight increase was expected. Cutler [2] also stressed the rarity of the normal sedimentation rate in the presence of clinically active disease. On the other hand, few of the studies dealing with the sedimentation rate

in specific diseases show invariable increase in the sedimentation rate in any single disease. Even in active pulmonary tuberculosis, 7.35 per cent of 2,000 cases showed a normal sedimentation rate.[13] The following cases are examples of those in which an elevated rate was expected, and a normal rate obtained.

Case 1. L. O., a widow, aged 59, entered the Diagnostic Hospital on January 25, 1937. She had been in good health prior to July 1935, when she noticed a mass in her left breast. One year later she consulted a physician; a radical mastectomy was performed; and the structure of the growth showed it to be scirrhous carcinoma. In November 1936, four months after the operation, she noted several masses in the region of the scar. There had been no weight loss, or other complaints.

Examination revealed numerous hard, non-tender, nodular masses lying along the operative scar. There was no localized tenderness. There were several small, firm, supraclavicular nodes on the left. The examination was otherwise negative, and no evidence of other metastases was noted. There was no anemia. The blood sedimentation rate was 5 millimeters in one hour. (Incidently, many of our unexpectedly normal rates appeared in patients with cancer.)

Case 2. I. L., a single male, aged 29, was admitted to the Diagnostic Hospital on Oct. 11, 1932, complaining of slight non-productive cough, a loss of 10 lbs. in weight, easy fatigability, and increased irritability. A year and a half previously he had been told that he had an arrested tuberculosis. Physical examination was negative with the exception of evidence of weight loss. Roentgen-ray examination of the chest showed a moderately extensive parenchymal involvement at the apex of the right lung. There was no clinical or laboratory evidence of activity. The blood sedimentation rate was 2 millimeters in one hour on two occasions. He gained 20 pounds during one month, and was discharged.

He returned to the Hospital on June 2, 1937. He had been well until a few months before admission, when he had an occasional slight elevation of temperature. The physical examination was again negative. Roentgen-ray examination showed an active lesion in the apex of the left lung, which had not been present at the time of the first examination. Over a period of two months this infiltration showed definite regression, confirming the diagnosis of an active process at the time of admission. The blood sedimentation rate was not above four millimeters in one hour, on four determinations.

There were, of course, cases in which the sedimentation rate was elevated, but a normal sedimentation rate would have been predicted following the admission history and physical examination. In many cases this fact led to a more extensive search, and evidence of a disease usually associated with an increased sedimentation rate was found. It is in just these cases that the routine blood sedimentation test is of great help, since an unexpectedly elevated rate leads to a more intensive search for evidence of disease.

Significance of an Elevated Sedimentation Rate in Relationship to the Type of Disease. Elevation of the blood sedimentation rate in a case in which there is no evidence of an organic disease usually associated with such an increase may be as misleading as an elevated rate in a case without evidence of disease. In our series there were 738 cases of organic disease of a type usually associated with a normal sedimentation rate. In this group

85 cases, 11.6 per cent, showed an increased sedimentation rate. In a similar group of cases, Hirsh [11] reported that of 283 determinations that should have given a normal rate, only 11 (3.8 per cent) showed accelerated rates. Wintrobe [12] observed that in a number of instances of infection in which slight or moderate increases were expected, high values were obtained.

The records of the 16 patients with definitely elevated rates were reviewed. The fact that only four were males is again striking. Of the 16 cases, organic disease was present in 14. One patient was a 14 year old girl, discharged with a diagnosis of "lumbago," and the second will be discussed in more detail below. Of the remainder, 12 were discharged with a diagnosis of either hypertensive cardiovascular disease, or arteriosclerotic heart disease. Cases of this type were placed in the group in which rapid sedimentation rates were not expected largely on the basis of the variation of opinion as to the expected rate, as summarized by Wood.[14] Certainly some of these cases belong in the group in which rapid rates would be expected, according to his findings.

As noted above, an increased sedimentation rate occurred in 21 cases in which no evidence of organic disease was discovered, and in 85 cases in which evidence of an organic disease usually associated with a normal sedimentation rate was found. These two groups represent 106 cases, 5 per cent of the series, in which an increased sedimentation rate was misleading. Therefore, in our series, a sedimentation rate of more than 20 millimeters in one hour was indicative of an organic disease of a type usually associated with an increased sedimentation rate in 95 per cent of the cases. The following examples are representative of the group in which no evidence of an organic disease usually associated with an increased sedimentation rate was discovered, but in which the rate was increased.

Case 3. D. S., a widow, aged 67, entered the Diagnostic Hospital on April 30, 1934, complaining of abdominal pain following meals, which had been present for one year. There had been occasional vomiting, constipation, dyspnea on exertion, and nocturia for several years. There was slight upper abdominal tenderness, and the blood pressure was 210 mm. mercury systolic and 120 mm. diastolic. The red blood cells numbered 3.7 million per cubic millimeter of blood, and there was slight leukocytosis. The urine contained a small amount of albumin. Study of the colon following a barium enema showed diverticuli of the sigmoid colon. Study of the stomach, small intestine, and gall-bladder was negative. The blood sedimentation rate was 118 millimeters in one hour. She was discharged on May 16, 1934. None of the findings would explain such a greatly elevated sedimentation rate.

Case 4. V. L., a single male, aged 38, was admitted to the Diagnostic Hospital on April 24, 1936 complaining of pain in the lower abdomen. Two days before admission he developed mid-abdominal pain which shifted to the right lower quadrant of the abdomen. There had been no nausea, and several bowel movements followed a laxative. On admission the temperature was 99.2 degrees; there was a moderate leukocytosis; and the sedimentation rate was 39 millimeters in one hour. There was local tenderness on pressure in the right lower quadrant of the abdomen.

He was observed for several days. On the second day the temperature was normal; the pain had disappeared; and the white blood cell count had declined. However,

the sedimentation rate had increased to 43 millimeters in an hour. Four days after admission he was feeling perfectly well, the temperature and white blood cell counts were normal, but the sedimentation rate remained unchanged. On the fifth day roentgen-ray examination of the gastrointestinal tract showed no unusual findings, but the sedimentation rate had risen to 65 millimeters in one hour. He was discharged with a diagnosis of subsiding appendicitis and was kept under observation.

On May 5, one week after discharge, he was feeling well. There was slight leukocytosis, and the sedimentation rate was 36 millimeters in one hour. On May 28, his appendix was removed. There was no evidence of other intra-abdominal disease, and the appendix showed changes in structure consistent with a diagnosis of subsiding acute inflammation.

The patient has remained well up to the present time. It has been emphasized by Lesser and Goldberger [15] that the sedimentation rate in appendicitis is not increased, and no evidence of other disease usually associated with an increased sedimentation rate was discovered in this case.

The Sedimentation Rate in Cases in Which Other Routine Laboratory Procedures Were Negative. Certain cases showed normal results on all of the following routine laboratory procedures: Hinton, Wassermann, and Kahn tests, urinalysis, and white blood cell count. These cases, 1063 in all, were divided into "positive" and "negative" groups according to diagnosis, and the blood sedimentation rates were related to the two groups, as shown in table 5.

TABLE V

Relationship of the Sedimentation Rate to the Diagnosis in Cases in Which Other Routine Procedures Were Negative

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0–15	16–20	21–30	31+		
Diagnosis Positive						
Male	187 55.9%	36 10.7%	34 10.1%	77 23.3%	334	111 33.4%
Female	181 52.7%	47 13.7%	52 15.1%	63 18.5%	343	115 33.6%
Totals	368 54.3%	83 12.2%	86 12.7%	140 20.8%	677	226 33.5%
Diagnosis Negative						
Male	146 95.4%	6 3.9%	1 0.7%	0	153	1 0.7%
Female	212 91.0%	12 5.1%	6 2.6%	3 1.3%	233	9 3.9%
Totals	358 92.7%	18 4.6%	7 1.8%	3 0.9%	386	10 2.7%

The blood sedimentation rate was elevated in 226 of the group of 1,063 cases showing negative results on other routine laboratory procedures, 10.9 per cent of the entire series. It seems reasonable to conclude that, in these cases, the presence of disease would have been overlooked, from a laboratory standpoint, if the blood sedimentation test had not been performed as a routine diagnostic procedure. Ten cases of the group, 0.5 per cent of the entire series, showed an increased rate but no discovered evidence of organic disease.

Relationship of the Blood Sedimentation Rate to Anemia. In recent years much emphasis has been placed on the necessity for correction of the sedimentation rate for anemia. Several methods for determination of the sedimentation rate have been advocated because of the relative ease with which they may be corrected for anemia.[16, 17] There is agreement that, in general, the sedimentation rate bears an inverse proportion to the volume percentage of the red blood cells. Wintrobe [5] and Bannick et al.,[8] among others, have pointed out that the "corrected" sedimentation rate may be misleading, in a case in which the uncorrected rate may be given a more nearly correct index of the condition of the patient. Gregg [18] reported the results of sedimentation tests on rabbits made anemic by bleeding, and found that they were less rapid than the values derived from the dilution experiments upon which charts for correction of the sedimentation rate for anemia are based. Bannick et al.[8] observed that the sedimentation rates in cases of bleeding from duodenal ulcer were usually not increased as much as the degree of anemia would have led one to expect. Bouton [19] concluded that in a case with anemia with essentially normal findings otherwise but with a definitely pathological sedimentation curve, the true disease had not been determined and was of serious nature. He also advanced the interesting idea that correction for anemia gives a false accuracy to a procedure which is essentially non-specific and which yields only approximate values. Cutler et al.[20] concluded from a critical appraisal of both experimental and clinical observations that anemia has little to do with the phenomenon of blood sedimentation. Our findings are in agreement with this statement.

The sedimentation rates in our series had not been corrected for anemia. The non-specific nature of the phenomenon had been recognized, and the blood sedimentation test had been considered as something of a "laboratory impression." In a diagnostic study the presence of anemia was considered to be of importance, either as the primary disease or as a manifestation of the primary disease. Therefore, a rapid sedimentation rate reflecting the presence of anemia alone is of importance when the test is used as a routine procedure. Also, the added complexity of the test, if correction of anemia is considered essential, is probably responsible in part for the infrequency with which the test is used as a routine laboratory procedure. In our series of cases there were 186 cases showing a definite anemia, that is, with less than 3.5 million erythrocytes per cubic millimeter of blood. The sedimenta-

tion rates in these cases were related to the degree of anemia, and the results were tabulated in table 6.

In the group of 186 cases showing a definite anemia, 69 cases, 37 per cent, showed a normal sedimentation rate. Even 7 of the 18 cases showing

TABLE VI

Relationship of the Sedimentation Rate to the Red Cell Count in Cases with Anemia

Red Cell Count	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81+	Total
3,500,000 to 3,100,000...	24	17	11	6	3	12	5	2	15	95
3,000,000 to 2,600,000...	5	8	10	4	1	3	3	0	10	44
2,500,000 to 2,100,000...	3	5	4	0	4	1	4	0	8	29
2,000,000 and below....	2	5	1	3	1	1	1	0	4	18
Totals.....	34	35	26	13	9	17	13	2	37	186

a red blood cell count of less than two million cells per cubic millimeter showed a normal sedimentation rate. These findings represent a strong argument against the necessity for the correction for anemia when the sedimentation test is used as a routine procedure. The following cases are examples of this group.

Case 5. W. T., a white male, aged 66, was admitted to the Diagnostic Hospital on October 18, 1937, complaining of loss of appetite, weakness and jaundice of six months' duration. Examination revealed a stuporous, emaciated, icteric, pallid man. There was absence of the vibratory sense over the lower extremities; the tongue was smooth and red; and the spleen was not palpable. Laboratory studies showed a histamine achlorhydria, a red blood cell count of 980,000 cells per cubic millimeter, and a hemoglobin level of 4.6 grams per 100 cubic centimeters of blood. There were numerous macrocytes, and the red blood cells were hyperchromic. The serum proteins were 3.66 per cent, albumin 2.28 per cent, and globulin 1.38 per cent. The mean corpuscular volume was 113 cubic micra. The blood sedimentation rate was 7 millimeters in one hour. He improved steadily under appropriate therapy with liver extract.

Case 6. M. L., a white widow, aged 54, was admitted to the Diagnostic Hospital on September 1, 1937. Over a period of 18 months she had gradually developed weakness, anasarca and orthopnea. Her diet had been grossly deficient, consisting largely of bread, potatoes, and rice for two years. Examination revealed a pallid, dyspneic, edematous woman. There was slight cardiac enlargement, marked edema of the feet and ascites. There were 1,560,000 red blood cells per cubic millimeter of blood, and the hemoglobin level was 2.5 grams per 100 cubic centimeters of blood. The mean corpuscular volume was 75 cubic micra. The blood sedimentation rate was 18 millimeters in one hour. She showed striking improvement, with an adequate diet and iron.

Relationship of the Sedimentation Rate to the White Blood Cell Count. There is general agreement that variations in the total leukocyte count bear no direct relationship to the sedimentation rate; but the average count is often slightly higher in cases with a rapid rate, because of the relationship of both

factors to a number of diseases.[21] This partial parallelism has been used as an argument against the need for the use of the sedimentation test as a routine procedure.

The cases in this series were divided into a group in which the white blood cell count was elevated and another in which the white cell count was normal. A count of more than 10,000 leukocytes per cubic millimeter of blood was considered abnormal.[22] The sedimentation rates of the two groups of cases were then tabulated, and the results are shown in table 7.

TABLE VII

Relationship of the Leukocyte Count and Sedimentation Rate

W.B.C. Count per Cubic Millimeter	Sedimentation Rates—mm. per hr.				Total Cases	Total Cases Elevated Rates
	0–15	16–20	21–30	31+		
10,000 or above.....	233 45.3%	40 7.7%	57 11.1%	184 35.9%	514	241 47.0%
Below 10,000.....	938 60.5%	140 9.0%	176 11.3%	295 19.2%	1549	471 30.5%

This study showed that 47 per cent of the cases with an increased white cell count showed an increased sedimentation rate. However, 30 per cent of those with a normal white cell count showed an increased rate. This indicates that the apparent parallelism between increased sedimentation rate and increased white cell count is not sufficiently marked to permit the exclusion of the one test when the other test is performed routinely.

Relationship of the Sedimentation Rate to Sex. In considering the normal sedimentation rate, it was formerly customary to assign a slightly higher rate to women than to men.[7] Rourke and Ernstene [16] expressed the opinion that the faster rate in women was due to the lower normal hematocrit value. Wintrobe [17] also stated that the difference was due largely to quantitative difference in the total number of cells. Our observations develop one further fact as regards the sedimentation rates in males and females, namely, that among females there are more misleading accelerated rates than among males. In all, 32 males, 3.2 per cent of the series, showed an increased rate when no evidence of an organic disease usually associated with an increased rate was discovered. Among the females, however, there were 74 such cases, 6.9 per cent of the group.

The Sedimentation Rate in Occult Disease. One of the most important reasons for the use of the sedimentation test as a routine procedure is that it may call attention to the presence of more or less occult disease. The following cases are illustrative:

Case 7. M. P., a white, married male, aged 39, was admitted to the Diagnostic Hospital on April 27, 1935, complaining of pain in the back, abdominal pain, tiredness,

loss of weight, and numerous other symptoms. The upper abdominal pain was the most constant symptom, coming on about five minutes after the taking of food. Tiredness was so marked that it was not alleviated by 18 hours of sleep. He had not been well since 1912, and had developed abdominal pain as early as 1918. Physical examination showed obesity and, with the exception of slight lower abdominal tenderness, was negative. The diagnosis at this time was psychoneurosis.

The urine was normal, and there was no anemia. All other studies, including roentgen-ray examination of the gastrointestinal tract, were negative. The blood sedimentation rate was 58 millimeters in one hour, and remained above 50 millimeters on four subsequent determinations. He complained of severe abdominal pain throughout the period of observation, but without definite physical findings. He was discharged on May 3, 1935. It was thought that most of his symptoms were due to psychoneurosis, but, because of the increased sedimentation rate, the question of retroperitoneal abscess or neoplastic growth was raised, and an interval study was advised.

Two days after discharge, the patient experienced more severe abdominal pain, and a mass was palpated in the left upper quadrant of the abdomen. Laparotomy showed a large carcinoma of the tail of the pancreas which involved the neighboring peritoneum and contained a large recent hemorrhage.

Case 8. E. L., a Russian male, aged 47, was admitted to the Diagnostic Hospital on May 25, 1933 complaining of abdominal cramps. He had noticed abdominal distention and slight lower abdominal pain 12 weeks before admission. The pain had become more troublesome during the nine days before admission. He had lost his job six months previously and had been drinking rather heavily since that time. Physical examination was negative with the exception of upper abdominal tenderness which disappeared when his attention was distracted. There was no anemia or leukocytosis. The blood sedimentation rate was 41 millimeters in an hour. He wept at the prospect of returning home. He was discharged on June 1, 1933, with the diagnoses of psychoneurosis and essential hypertension.

Three days after discharge, the abdominal pain became more severe and he was admitted to another hospital. Examination and laboratory studies were similar to the previous studies, but the blood sedimentation rate was not determined. The emotional instability was marked and it was concluded that much of his unhappiness was of psychic origin. The white cell count was found to be 20,000 per cubic millimeter. He died on June 7, 1933, four days after admission. Postmortem examination showed thrombosis of the superior mesenteric artery with gangrene of the ileum. The thrombus showed organization, old and recent. There was also an organized thrombus of the inferior mesenteric artery, with infarction of the small and large bowel.

Summary

The blood sedimentation test was used as a routine laboratory procedure in 2063 unselected cases of general diagnostic problems. A modified Westergren technic was employed; the reading at the end of one hour was considered to be the significant reading; the rate was not corrected for anemia; and a rate of more than 20 millimeters in one hour was considered abnormal. The presence of organic disease was indicated in 702 cases, or 34.1 per cent of the series, by a sedimentation rate which was elevated.

Of all the cases with definite evidence of organic disease (1549), 43.9 per cent, or 681, had elevated rates. Of those cases without evidence of organic disease (514), only 4.0 per cent had elevated rates. Because cer-

tain types of organic disease produce an increase in the sedimentation rate, while other types do not, these two general types of organic disease were separately analyzed. Of the cases with evidence of disease usually associated with an increased sedimentation rate, 73.5 per cent showed elevated rates. Those with evidence of a disease usually associated with a normal rate showed increased rates in 11.6 per cent. A normal sedimentation rate did not exclude the presence of the type of disease usually associated with an increased blood sedimentation rate. A sedimentation rate of more than 20 millimeters in an hour was indicative of organic disease of a type usually associated with an increased rate in 95 per cent of the cases. In 226 cases, 10.9 per cent, the blood sedimentation rate was elevated and other routine laboratory procedures were negative. Only 10 of these 226 cases had no discovered organic disease.

In a group of 186 cases showing anemia of less than three and one-half million red cells per cubic millimeter, 37 per cent showed a normal sedimentation rate. An elevated sedimentation rate and an elevated white blood cell count are not necessarily parallel findings.

The presence of an increased sedimentation rate in males showing no evidence of disease was noted in only one case. In general, an increased rate in the male was more likely to be present with a disease usually associated with an increased rate than in the female. The value of the routine use of the sedimentation test as an indicator of occult organic disease is noted.

Conclusion

The blood sedimentation test performed by a simple method, without correction for anemia, is of value as a routine diagnostic procedure.

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THE IMPORTANCE OF ALLOWING TIME FOR "PHYSIOLOGICAL ADJUSTMENT" IN ESTABLISHING THE DIET IN DIABETES*

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The term "physiological adjustment," as here used, refers to the way in which the physiological processes respond to the demands of carbohydrate metabolism. In the normal individual this adjustment is so prompt and efficient that even widely varying amounts of glucose are utilized almost immediately; in fact it is difficult to break through a normal glucose tolerance. In the diabetic, on the other hand, physiological adjustment is sluggish and lacks quick mobility; therefore, it can become fully effective only when the demands upon it are reasonable, and are maintained unchanged day after day until adjustment has had time to complete itself.

Several factors enter into this slowing up of the rate of physiological adjustment in the diabetic: the fundamental cause, of course, is the reduction in the capacity to utilize glucose. However, in previously untreated cases, another factor is superimposed in that the prolonged high blood sugar further depresses the already impaired glucose tolerance, and thus temporarily exaggerates the severity of the diabetes. Because of the variability of this second factor, it is almost impossible to determine the true severity of a case of diabetes in advance of treatment; and, for the same reason, the time required for physiological adjustment to a suitable régime cannot be predicted.

For example, in figure 1 are plotted the blood sugar determinations of two patients, under almost identical dietary régimes. One patient (Mrs. K.) responded unusually promptly, the blood sugar dropping to 160 in three days and on down to 120 in eight days from the beginning of the diet. The other patient responded much more slowly, requiring about three weeks to attain the tolerance that Mrs. K. showed in five days. And yet, curiously enough, Mrs. K., who responded so quickly, seemed to be a much more severe diabetic, as judged by the history, for she had lost weight, was bothered with polyuria, weakness, and itching, and had a sluggish ulcer on the ankle. Comparison of these two patients illustrates the variability of time for physiological adjustment, and the difficulty of predicting the severity of the disease.

Two conditions are essential if physiological adjustment is to develop in a favorable direction: (1) the diet must be reasonably close to the eventual tolerance of the patient, or, in the severe cases, to the insulin dosage; and (2) there must be consistent regularity day after day, not only of the diet,

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but also of such habits as hours of sleep, exercise, and the time of meals. Indeed, it is likely that the process of adjustment involves not only the metabolic activities, but also, to some extent, the functions of digestion which are so responsive to regularity of routines.

Despite its sluggishness, physiological adjustment usually begins promptly, if a correct dietary formula has been instituted, and an improving glucose tolerance may be evident within 24 to 48 hours. But, this improve-

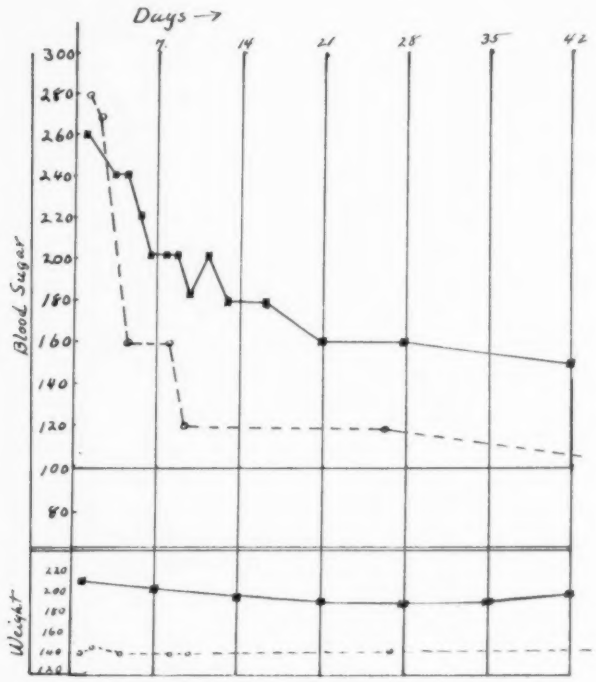

FIG. 1. Blood sugar levels of two patients under almost identical dietary régime; no insulin.

○- - -○ = K., female, aged 60;
diet: C.H. 120, Prot. 65, Fat 90; calories 1550
■——■ = B., female, aged 72;
diet: C.H. 115, Prot. 65, Fat 100; calories 1620.

In both cases the diet remained unchanged throughout the above recorded periods. Note the difference in the rate of the "physiological adjustment," "K" being more rapid, despite the fact that she presented more severe symptoms at the beginning of treatment.

ment is only a beginning, and if the carbohydrate intake is maintained unchanged, the blood sugar levels will show a further downward trend until the adjustment is completed, the time required for this varying from two or three days to as long as several weeks. While this downward trend is usually a steady one, with the utilization of glucose a little better each day, in occasional cases the improvement seems to take place in a series of abrupt steps, each after several days of more or less stationary conditions. Whether the adjustment proceeds smoothly, or by a series of steps, one can recognize

when it is complete by the fact that thereafter the blood sugar findings remain essentially the same day after day. It is only at this stage that one can judge whether or not a trial diet is suitable. If further changes are indicated, each change in the carbohydrate allowance is again followed by a period of physiological adjustment, which may be just as long as the preceding one. In brief, any change in the diet or insulin régime of a diabetic, whether the change is instituted at the beginning or in the midst of treatment, requires time for effective physiological adjustment; and the length of this time requirement cannot be predicted.

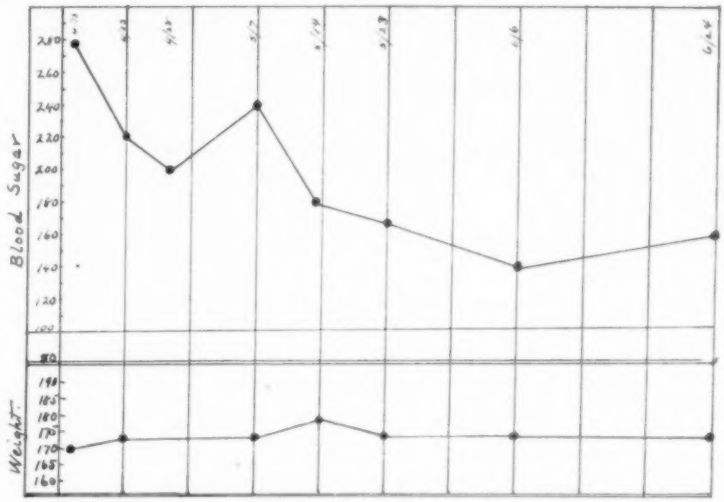

FIG. 2. Unusually slow "physiological adjustment."
Male, aged 57. Diet: C.H. 110, Prot. 80, Fat 100; calories 1660. Diet unchanged throughout the above period. No insulin.

An example of a fairly prolonged period of adjustment is shown in figure 2, the patient slowly developing an increasing tolerance, so that in four weeks he was utilizing practically all of an adequate diet, without insulin, and in six weeks his post-prandial blood sugar was normal. In this case the adjustment was unusually slow, but nevertheless the trend toward improvement was evident almost at once by the reduction in the blood sugars, taken in each instance one hour after lunch. The only treatment in this case was strict adherence to the diet (C.H. 110, Prot. 80, Fat 100; calories 1660), the patient continuing his ordinary business activities throughout. One can see that if the findings at the end of the first or second week had been accepted as the basis for further changes, insulin would probably have been given. Although the use of insulin prematurely would not have been disastrous in this case, it would certainly have resulted in additional weeks or even months of juggling of insulin and dietary formulae before eventual stabilization was attained.

It is not within the purpose or scope of this paper to discuss in any detail the various theories that might explain this time lag in the metabolism of carbohydrates in diabetes. However, there are several well recognized features of the carbohydrate metabolism in normal individuals that probably have a direct bearing on this matter, and are therefore presented very briefly and without any attempt to refer to the extensive literature on the subject. These features are: First, the presence of glucose in the blood, or body fluids, apparently acts as either a stimulus or an aid to the utilization of glucose. This effect is evident under the following conditions: (*a*) in an ordinary glucose tolerance test the blood sugar will drop in two to four hours to a level considerably lower than it was just before the glucose was administered. Occasionally this drop is sufficient to cause a mild hypoglycemic reaction. Indeed, mild diabetics seem to be especially prone to these hypoglycemic reactions after taking an unaccustomed amount of carbohydrate. (*b*) After prolonged fasting (three to five days) ingestion by a normal individual of an average amount (50 gm.) of glucose will result in an abnormally high rise in the blood sugar (200 mg. or even more). Apparently, during the prolonged fast, throughout which there is characteristically a low blood sugar, the mechanism for the utilization of glucose is partially lost and is not immediately recovered on the sudden appearance of glucose in the blood. (*c*) Again, if two successive doses of glucose are given, one or two hours apart, the rise of the blood sugar following the second dose is much less marked than that following the first. (*d*) Finally, a sustained, excessive demand on the carbohydrate utilization processes eventually causes their exhaustion, with a corresponding reduction in the glucose tolerance.

These well known features of the response to glucose ingestion indicate that the presence of glucose in the blood activates some mechanism for the removal of glucose from the blood; and, when this mechanism is partially lost by disuse, as in starvation, it requires an appreciable time to be brought into full play. Moreover, this mechanism can be exhausted by over-stimulation by as excessive glucose in the blood, and when thus exhausted, recovery is slow.

Second: a further and perhaps even more important element in the time factor in carbohydrate metabolism is found in the complex nature of the processes, in which the rôle of insulin is not entirely understood. Apparently there is an interaction between the pancreas, liver, adrenals, pituitary and tissues, calling for the elaboration of internal secretions and specific enzymes all of which enter into complex building up and breaking down of various forms of carbohydrate. In view of the interdependence of these internal secretions and the well known response of all glands to repeated, or "conditioning" stimuli, it is not surprising that a consistent but reasonable demand on the carbohydrate mechanism will result in a steady increase in sugar tolerance, but that when they are impaired, as in diabetes, ample

time must be given for all these complex processes completely to adjust themselves to demands.

Whatever the metabolic background may be, the fact is that the time requirements of physiological adjustment must be given due consideration, if a correct dietary régime is to be worked out without confusion. One should proceed along some such system as the following: Begin with a diet based on the ideal weight, i.e., a diet which, if it could be utilized, would maintain the patient in a state of normal, healthy activity. Having established this ideal diet, it is adhered to without change, day after day, until its effects can be accurately evaluated. A daily record is kept of the body weight and urinary glucose (if any); and blood sugar determinations are made often enough to show their trend. On the basis of these data, one can usually judge within 48 hours whether or not physiological adjustment in a favorable direction will take place. As long as there is some improvement, as shown by a diminishing urinary glucose and dropping blood sugar, even though this be slight, no dietary change should be made. Indeed, if the utilization of glucose merely holds its own, one should wait at least a few days, to see if the adjustment might develop by a series of abrupt steps rather than the usual gradual adaptation.

In certain instances, of course, it will soon become evident that the diabetes is so severe that there is no hope of effective adjustment to the prescribed diet. The next step in these cases is to begin insulin, in a dosage based on the amount of glucose lost in the urine. With the institution of the insulin régime, the same policy of watching for signs of adjustment should be followed, for even when aided with insulin the metabolic processes adapt themselves to the new régime slowly, and to make changes prematurely in either the insulin dosage or the carbohydrate intake leads to confusion.

In all cases in which adjustment is proceeding in a favorable direction, or, to express it in another way, in which the glucose tolerance is rising, one cannot predict where the adjustment will stop. The rule should be to wait until improvement has ceased, as shown by a tolerance that is stabilized for several days or longer. Then, if the blood sugar is not within the normal limits, the necessary changes, whether in diet or insulin, are instituted, after which one again waits for effective adjustment to take place. It is evident that working out the correct diet for a diabetic requires not only observation and judgment, but, above all, patience, and that the rule "make haste slowly" is especially applicable.

Conclusion

There is a very definite time requirement for a complete adjustment to any dietary change in diabetes. This time requirement varies from a minimum of three or four days to a maximum of as much as several weeks.

Therefore, with every change in the carbohydrate régime, the new formula should remain fixed for at least three or four days (barring emergencies) or longer if evidence of improvement continues. When the improvement ceases another change, if necessary, can then be made, this to be again followed by a period of watchful waiting. Such a policy of consistent, unhurried control offers the best chance of ultimate success in the treatment of diabetes.

PULMONARY EMPHYSEMA; A STUDY OF ITS RELATION TO THE HEART AND PULMONARY ARTERIAL SYSTEM *

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THE effect of emphysema on the pulmonary circulation and its secondary influence on the heart continues to be a controversial subject. On the basis of the earlier necropsy examinations, the general opinion became well established that emphysema produced a barrier within the pulmonary circulation which led to hypertrophy of the right ventricle and frequently to congestive heart failure. This opinion gained general approval but in recent years considerable doubt has been raised concerning this previously established view. The historical background of this problem has been reviewed so excellently in a recent paper by Parkinson and Hoyle [1] that it is only necessary for me to cite a few of the more recent investigations.

Griggs, Coggin and Evans [2] found hypertrophy of the right ventricle in 30 per cent of the cases of emphysema studied. On the other hand, Alexander, Luten and Kountz [3] found little evidence of cardiac involvement in a clinical study of a series of 50 patients with asthma and emphysema of long standing. In a later paper, Kountz, Alexander and Dowell [4] stated that, by roentgenologic examination, enlargement of the heart was demonstrated in only eight of 66 cases of advanced emphysema. Parkinson and Hoyle examined 80 patients with emphysema with special regard to the size and silhouette of the heart as determined by roentgenologic methods. They found that the heart as a whole was not enlarged in cases of uncomplicated emphysema. Localized enlargement of the cardiac silhouette was noted in 40 per cent of the cases and involved most often the conus pulmonalis of the right ventricle. They concluded, however, that the cardiac factor in emphysema seldom is pronounced except late in the disease and then not always and not unless there is other associated cardiac disease.

It is interesting to note that from their roentgenologic study Alexander, Luten, and Kountz concluded that the cardiac factor in emphysema was negligible; yet in the more recent investigation by Kountz, Alexander, and Printzmetal [5] both right and left ventricular enlargement were found at necropsy in 10 of 17 cases of emphysema. After the experimental production of emphysema in dogs similar cardiac enlargement occurred.

If it is assumed that emphysema may produce strain on the right ventricle, it follows either that there is an increased resistance in the pulmonary vascular bed producing intrapulmonary hypertension or that the strain on the heart is consequent to a demand for an increased pulmonary circulation in an effort to overcome the defective error in ventilation. An increased resistance in the pulmonary circuit in emphysema long has been assumed and

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explained on the basis that the result of alveolar distention is obliteration of the capillaries with obstruction to the flow of blood from the right to the left ventricle.

Investigations of the pulmonary circulation time in emphysema have been made in an effort to demonstrate the presence or absence of an increased resistance in the pulmonary circuit. Kountz, Pearson and Koenig [6] measured the circulation time through the lungs by injecting a dye into the right side of the heart of dogs with emphysema and recorded the interval of time before it appeared in a peripheral artery. They found no abnormal delay and concluded that there was no obstruction to the flow of blood through emphysematous lungs.

The studies of Weiss and Blumgart [7] were made by injecting a radioactive substance into the vein of one arm and measuring the interval before the emanation was detectable in the other arm. They found that only in far advanced cases of emphysema was the pulmonary circulation slowed. The conclusions drawn from these investigations are open to considerable doubt as far as their ability to indicate absence of resistance in the pulmonary circulation is concerned. It has been impossible as yet to prove a delay in the systemic circulation of patients with compensated hearts and systemic hypertension when an increased peripheral vascular resistance certainly exists. It, therefore, does not seem plausible to assume an absence of pulmonary circulatory resistance when the pulmonary circulation time is within normal limits. There is yet another factor which has not been studied adequately as a possible influence in the production of pulmonary hypertension in emphysema, that is the presence of arteriosclerosis of the pulmonary vessels. In recent years interest in what yet remains a relatively rare condition, namely, the so-called primary or idiopathic pulmonary arteriolar sclerosis has been increasing. From the evidence now available, there can be no doubt that advanced sclerosis of the smaller pulmonary arteries and arterioles can provoke marked pulmonary hypertension with subsequent right cardiac hypertrophy and failure.[8] The etiologic features of this condition, however, remain a controversial subject.

Steinberg [9] made a careful anatomic study of pulmonary arteriosclerosis and included in his report 50 cases of emphysema. An analysis of his tables reveals that sclerosis of the pulmonary vessels was present to a relatively high degree. Further studies by Miller,[10] Moschcowitz [11] and more recently by Brenner [12] and by Kaltreider [13] indicate a rather frequent association of pulmonary arterial disease with advanced emphysema. This possible relationship between pulmonary emphysema and pulmonary vascular changes and their combined effect on the heart seemed worthy of additional investigation.

Method of Study

The material for this study was selected from cases in which postmortem examination revealed essential emphysema. All cases in which the clinical

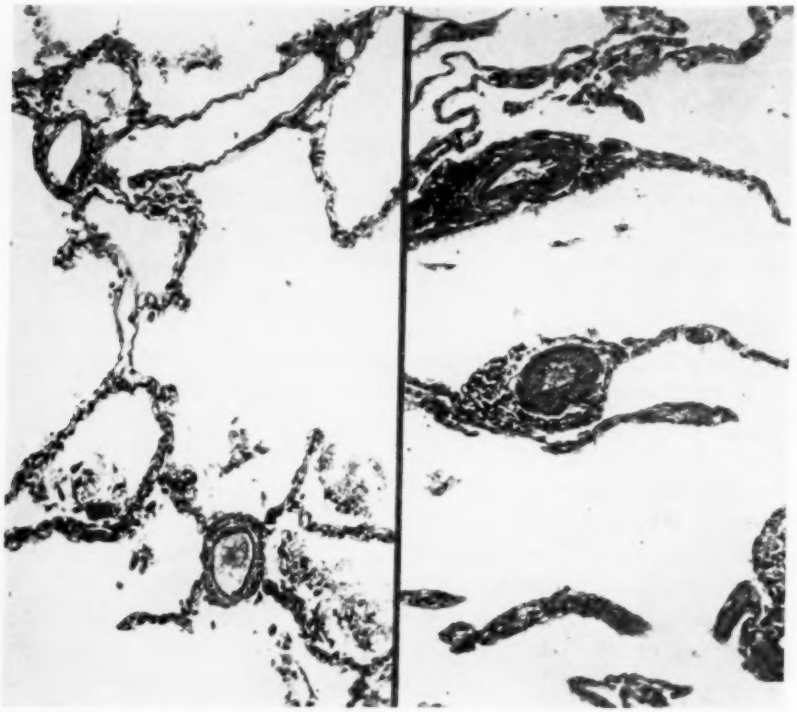
data gave evidence of hypertension, or the pathologic material evidence of valvular heart disease, pericarditis or other criteria of intrinsic heart disease which could have played a material part in determining the size and weight of the heart were discarded. In the cases selected for study the hearts were examined to determine the following data: weight and measurements of the thickness of the ventricles, including the minimal and maximal thickness of the muscle and the depth of the ventricles. From these measurements the degree of ventricular hypertrophy and dilatation was determined and recorded on the grading basis of O to 4 (grade O means no hypertrophy and is used for statistical purposes). The degree of coronary and aortic sclerosis was recorded.

The pulmonary artery and its main branches were studied grossly in all cases in which material permitted; in the other cases data as to the degree of gross pulmonary arteriosclerosis were obtained from the record of the necropsy. Sections from the different lobes of the lung were studied microscopically with regard to the pulmonary vessels. The degree of hypertrophy and thickening of the small muscular arteries was recorded, and representative arterioles from each section were selected and measured by means of a micrometer, according to the method of Kernohan, Anderson and Keith.[14] These measurements were compared to the ratio of normal wall to lumen in vessels of similar size, as determined by Kaump[15] in his study of normal pulmonary arterioles. By comparison of these figures it became possible to express the diameter of the lumen of each vessel as a percentage of that of the normal vessel and from all arterioles measured in each case the average diameter of the lumen is expressed as a percentage of that normally encountered. This figure, it is believed, best indicates the degree of narrowing or obstruction in the pulmonary arteriolar bed. Vessels in which the outside diameter was from 25 to 200 microns were considered as arterioles and are the ones included in these measurements.

It is well to mention at this point that on microscopic examination of the pulmonary arterioles marked variability was found with regard to the changes in the arteriolar walls. In some arterioles the increased diameter of the wall of the vessel was due predominantly to hyperplasia of the intimal layers whereas in others either in the same section or from the same lung hypertrophy of the media accounted for the increase in diameter of the wall. Furthermore these changes were not always symmetrical in a single vessel. A considerable variation in the degree of arteriolar narrowing also was noted in sections from the same case or even from the same lung (figures 1*a* and 1*b*). This fact is mentioned to emphasize the importance of the examination of several sections from the various parts of the lung and the careful measurement of representative arterioles from each section in order to compute with any degree of accuracy the total reduction in the arteriolar bed in any one case.

In analyzing the data obtained from the study of these cases, I have divided them into three groups, the basis for this division being the estimated

degree of pulmonary emphysema noted at the time of postmortem examination. All grading was made on the basis of 1 to 4; grade 1 denotes a minimal degree of emphysema, and grade 4 the most marked degree with severe diffuse emphysema of both lungs.



a *b*

FIG. 1. Marked variation in the degree of arteriolar narrowing which may be found in the same case and in the same lung; *a*, normal arterioles in a section from the lung (hematoxylin and eosin, × 125); *b*, advanced pulmonary arteriolar sclerosis in section from the same lung as *a* (× 90).

Cases of emphysema of minimal degree, or grade 1, were not included in this study. It was thought advisable to select for study only cases in which the diagnosis of emphysema was interpreted by the pathologist as one of the essential anatomic diagnoses. Minimal degrees of emphysema with emphysematous blebs or minor degrees of compensatory or senile emphysema are a frequent finding at postmortem examination and their presence is of doubtful, if any, significance from the standpoint of respiratory or circulatory physiology; therefore, only cases of essential emphysema of grade 2 or more were studied. The ages of these patients ranged from 40 to 70 years.

The 32 cases reviewed were divided into three groups. The first group consisted of cases in which the degree of emphysema present was of moderate

severity classified as grade 2 or 2+; the second group included cases in which the degree of emphysema was graded 3 or 3+; and the final group consisted of only four cases, in all of which a most extreme degree of emphysema was present and was classified as grade 4.

Correlation of Data and Comment

Certain interesting correlations may be made from the data accumulated.

Congestive Heart Failure in Emphysema. Of the 32 cases death from cardiac failure with decompensation occurred in 14 cases or 44 per cent (table 1). In four additional cases death resulted from cardiorespiratory

Table 1

Comparison of Cardiac Findings and Occurrence of Congestive Failure in the Various Groups

Class	Grade of hypertrophy	Group 1* (20 cases)	Group 2 (8 cases)	Group 3 (4 cases)	Total (32 cases)	
		Number	Number	Number	Number	Per cent
Right ventricle	0	7	1	0		
	1 2 3	4 7 2 } 13	1 3 3 } 7	1 0 3 } 4	24	75
	Median grade	1	2	3		
Left ventricle	0	15	3	3		
	1 2 3	4 1 0 } 5	4 1 0 } 5	1 0 0 } 1	11	34
	Median grade	0	1	0		
Average heart weight, gm.		383	461	377	402	
Per cent increase above normal * †		28	41	35	32	
Congestive failure	Number	6	5	3	14	
	Per cent of group	30	63	75	44	

* Group 1 consists of cases of emphysema, grade 2 or 2+. Group 2 of cases of emphysema, grade 3 or 3+ and group 3 of cases of emphysema grade 4.

† Based on calculation according to method of H. L. Smith.[25]

failure during severe attacks of asthma. The severity of the emphysema seemed to bear a direct relationship to the development of congestive heart failure, for there was a progressive increase in its occurrence in the more advanced cases of emphysema; for example, congestive heart failure occurred in 30 per cent of cases in group 1, in about 63 per cent of cases in group 2, and in 75 per cent of cases in group 3.

The development of cardiac decompensation secondary to pulmonary emphysema has been considered by numerous authors to be uncommon un-

less other causes for cardiac disease are present. It may seem, therefore, that its frequent occurrence in this study demands further explanation. In most cases of pulmonary emphysema in which death occurs from congestive heart failure there are no doubt additional factors concerned, for with the fifth decade of life and beyond, arteriosclerotic and hypertensive heart disease is common and calcified relics of old healed valvular disease may be seen also. These factors may be more predominant than the emphysema in producing cardiac failure. Attempt was made, however, to eliminate from this study all cases in which there was any other cause for cardiac failure than emphysema. It is, of course, obvious that cases of coronary sclerosis could not be excluded, for its occurrence in greater or lesser degree in the period of life at which our material was obtained is universal. The possible presence of previous hypertension which was not recorded clinically must also be considered as a factor in the development of congestive failure in some of these cases. Regardless of this possibility, the occurrence of congestive heart failure in such a large number of cases in which there was no other evidence of heart disease and in which the degree of coronary sclerosis was negligible leads to the conclusion that advanced emphysema not only occasionally but in a high percentage of cases leads to ultimate failure of the heart.

Weight of the Heart. There was a significant increase in the weight of the heart above normal in all three groups. This increase in the weight of the heart, however, was not directly related to the severity of the emphysema, for the average increase above the calculated normal was greater in group 2 than in group 3 (table 1).

Hypertrophy of the Right Ventricle. There was a consistent increase in the frequency of occurrence as well as in the degree of right ventricular hypertrophy in the more advanced cases of emphysema. In the first group the right ventricle was enlarged in 65 per cent of the cases, in the second group in 87.5 per cent, and in the last group in 100 per cent. That there was a consistent increase in the average degree of right ventricular hypertrophy is shown by the fact that in group 1 the median grade of right ventricular hypertrophy was grade 1, in group 2 it was grade 2 and in group 3 it was grade 3 (table 1).

Hypertrophy of the Left Ventricle. Attention should be called to the fact that an appreciable hypertrophy of the left ventricle occurred in 11 cases (34 per cent) but in none of these was the enlargement of the left ventricle relatively greater than that of the right. The finding of both left and right ventricular enlargement has been noted in other studies. The question arises, why should there be any hypertrophy of the left ventricle in emphysema when from the theoretic standpoint the strain of the circulation is on the right ventricle alone. It has been suggested that there is a partial asphyxia of the heart muscle as the result of faulty exchange of oxygen in the lung. Experimental work by Vacek [16] and by Strughold,[17] seems to give some support to this contention. It would seem, however, that the

finding of hypertrophy of the left ventricle in these cases represents a work hypertrophy and is explained most logically on the basis of hypertension in the systemic circulation which was not detected clinically.

Pulmonary Arteriosclerosis. On examination of the pulmonary arterial system it was found that in only six cases or 18.7 per cent were all the pulmonary arterial divisions normal. The frequency of arteriosclerosis in the pulmonary artery and its main tributaries did not seem to bear a direct relationship to the degree of emphysema. Gross atherosclerosis was noted in only one case in group 1 which included 20 cases; it was found in seven of the eight cases in group 2, but in only one of the four cases in group 3. On the other hand, the degree of arteriosclerotic involvement of the small muscular arteries increased with the severity of the emphysema. When the

TABLE II

Summary of Pulmonary Arteriolar Measurements

Emphysema	Group 1* (20 cases)	Group 2 (8 cases)	Group 3 (4 cases)
Without arteriolar sclerosis	10 (50%)	0	1 (25%)
With arteriolar sclerosis	10 (50%)	8 (100%)	3 (75%)
Measurement of arterioles, per cent† Minimum	75	60	65
Maximum	107	86	103
Average	91	70	76

* See footnote table 1.
† Measurements expressed in percentage of diameter of the normal lumen.

TABLE III

Comparison of Degree of Pulmonary Arteriolar Narrowing with (1) Hypertrophy of the Right Ventricle, (2) Degree of Coronary Sclerosis, (3) Sclerosis of the Aorta

	Reduction in the average diameter of the arterioles, per cent			
	0–9.9	10–19.9	20–29.9	30–39.9
Total number of cases	11	7	8	6
Hypertrophy of right ventricle, median grade on basis of 0 to 4	1	2	2+	1+
Coronary sclerosis, median grade on basis of 0 to 4	1+	1	1+	1+
Aortic arteriosclerosis, median grade on basis of 0 to 4	2	2	2	2

reduction of the diameter of the arteriolar lumen was compared with the degree of emphysema, it was found that in 21 cases or 66 per cent of the entire group there was a reduction in the average arteriolar lumen amounting to 10 per cent or more; in 11 or 34 per cent of the cases there was no sig-

nificant reduction, and in a few instances the average diameter of the lumen was more than that calculated for normal (tables 2 and 3).

In groups 2 and 3, which included the more advanced cases of emphysema, there was a greater incidence as well as a greater degree of narrowing in the arteriolar system. With the exception of a single case in group 3 in which there was no arteriolar obstruction, this relationship remained consistent.

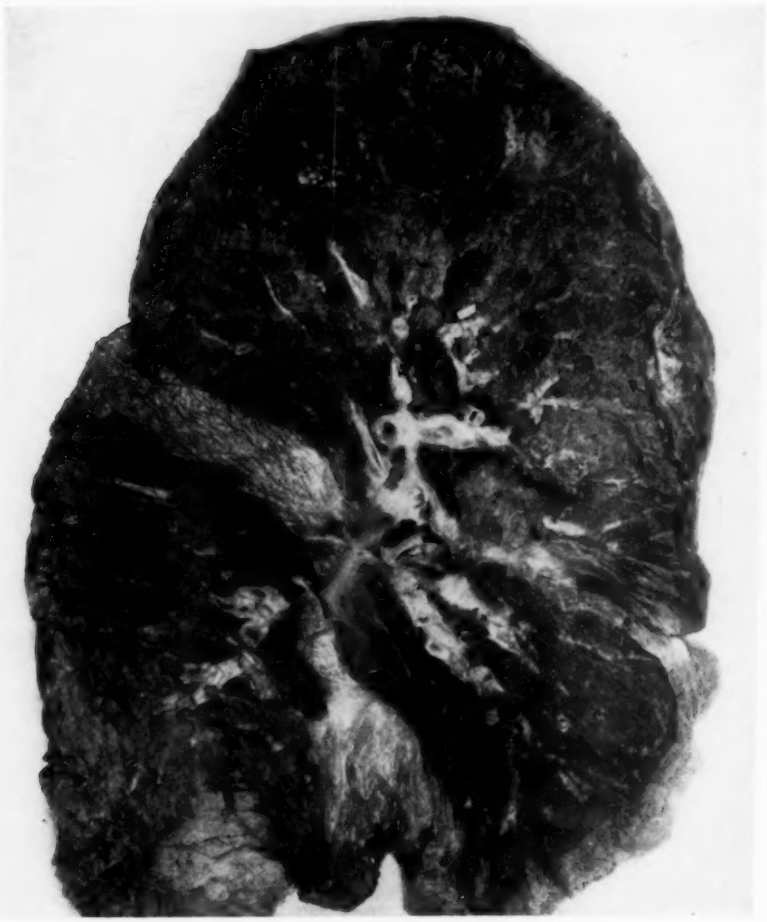


FIG. 2. Emphysema of lung, grade 4.

To appreciate fully the importance of these changes in the arteriolar system it must be remembered that the pulmonary arteriolar bed, like the remainder of the vascular system, is endowed with a vascular reserve in excess of that necessary to meet ordinary functional demands. Experimental studies have demonstrated that as much as 50 per cent of the pulmonary circulation can be shut off without marked variation in the general

circulatory condition.[18, 19] The healthy heart, no doubt, can accommodate itself to obstruction in the pulmonary arterial system provided this obstruction is not too diffuse and the remainder of the vascular bed can dilate and transmit an increased flow of blood. In emphysema a demand exists for increased pulmonary circulation to compensate for the defective error in ventilation and the heart can be expected to meet this demand only as long as the vascular reserve is not exceeded.

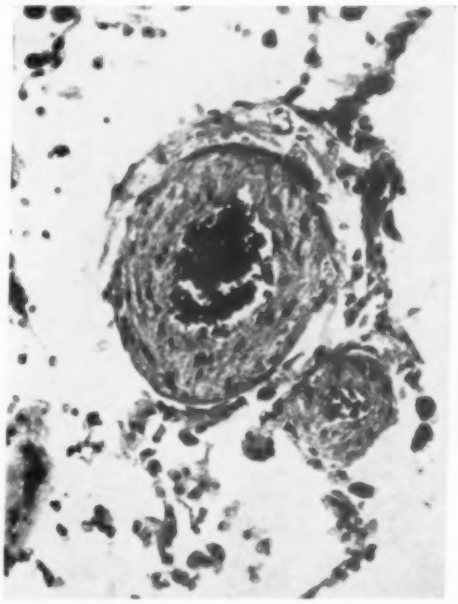


FIG. 3. Arteriole from same lung as shown in figure 2; marked hyperplasia of the medial layers may be noted. Diameter of the lumen approximately 60 per cent of normal (× 200).

In this series of cases an occasional case was seen in which the right ventricle had hypertrophied and failed and yet the arteriolar system seemed to present little or no obstruction. It must be assumed, therefore, that the vascular reserve of the lung may be exceeded as a result of capillary compression and destruction alone caused by the diffuse nature of the disease. In the majority of instances, however, secondary arteriosclerotic changes were found in the arterial and arteriolar systems which augmented the circulatory obstruction. If, in emphysema, the condition were not far enough advanced to provoke a real insufficiency in ventilation, the heart may compensate for the obstructive phenomenon, but when both factors, ventilation and circulation, are disturbed sufficiently, the heart sooner or later must fail (figures 2, 3, 4 and 5).

In view of the almost constant relationship between the degree of emphysema and the amount of obliteration of the arteriolar bed, and in view of the consistent increase in hypertrophy of the right ventricle in association

a *b*

FIG. 4*a*. Branches of the main pulmonary arteries. Moderate atherosclerosis may be noted; *b*, hypertrophy grade 3 of right ventricle. Note marked increase in the thickness of the ventricle which averaged 9 mm. in diameter.

with increase of severity of emphysema, there should be a direct correlation between the degree of arteriolar obliteration and the amount of hypertrophy of the right ventricle. This assumption is not true, for when the hypertrophy of the right ventricle in cases of minimal pulmonary arteriolar obliteration (10 per cent or less) is compared with that in cases of moderate to advanced pulmonary arteriolar obliteration (20 per cent or more) no increase is found in the frequency or degree of right ventricular hypertrophy in the latter cases (table 3). The presence of pulmonary arteriolar narrowing in emphysema, therefore, does not seem to affect the right ventricle as

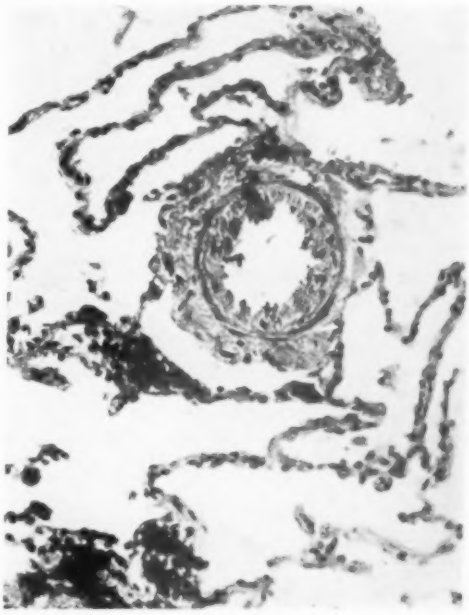


FIG. 5. Pulmonary arteriole showing irregular intimal and medial hyperplasia. Measurements of arterioles in this case revealed the average diameter of the lumen to be 73 per cent of normal. Section from same case as figure 4.

much as one would expect. The factors producing pulmonary hypertension in emphysema must exist then, whether or not arteriolar changes are associated. It is reasonable to assume that when arteriolar narrowing is advanced the pulmonary hypertension must be augmented, but it is doubtful whether the pulmonary arteriosclerosis seen in emphysema represents a primary change.

The question of the etiology of pulmonary arteriolar sclerosis is controversial. Various theories have been suggested. These are as follows: 1. The sclerotic change is a secondary manifestation of an already present hypertension in the pulmonary circuit and thus is a manifestation of the increased stress and strain on the pulmonary vessels.[11, 20] 2. The development of pulmonary arteriosclerosis is a secondary manifestation of pul-

monary infection.[21, 22, 23] 3. It may represent decrescent changes with age in a manner comparable with the changes in the systemic vessels. 4. There is a congenital predisposition or an inherent weakness of the vessels.[24] I shall not attempt to discuss the relative merits of these theories. It seems, however, from the findings just described that these changes when present in emphysema represent a secondary manifestation of an already present pulmonary hypertension which may best be explained by the compression and destruction of the capillary bed.

Steinberg has indicated that arteriosclerosis of the pulmonary vessels increases with advancing age in a manner similar to that in the systemic circulation. A close correlation might be expected, therefore, between the degree of pulmonary arteriosclerosis and the degree of sclerosis in the aorta and coronary vessels. When, however, the degree of aortic atherosclerosis (as graded on the basis of 1 to 4) is compared with the percentage reduction in arteriolar lumen, as high a median grade of aortic sclerosis is found

TABLE IV

Comparison of Cardiac Findings and Pulmonary Arteriolar Measurements in Relation to Congestive Heart Failure

	Grade	Cases	
		Congestive heart failure	No congestive heart failure
Right ventricular hypertrophy	0	0	8
	1	0	6
	2	7	3
	3	7	1
Left ventricular hypertrophy	0	7	14
	1	7	2
	2	0	2
	3	0	
Reduction in pulmonary arteriolar measurements, per cent	0– 9.9	3	8
	10–19.9	4	3
	20–29.9	4	4
	30–39.9	3	3
Total cases		14	18

in the group of cases without significant pulmonary narrowing (less than 10 per cent) as in that group in which the most marked narrowing of the pulmonary arterioles is present. There is also as high a median grade of coronary sclerosis in cases in which the reduction in the pulmonary arteriolar

lumen is minimal as in those in which pulmonary arteriolar sclerosis is most marked (table 3). These findings then indicate that pulmonary arteriolar sclerosis in emphysema is not representative of the degree of degenerative arterial changes in the systemic or coronary circulation. This lends further support to the opinion that these changes in the pulmonary arterioles associated with emphysema are secondary manifestations of pulmonary hypertension.

Another interesting correlation can be made if the cases of emphysema in which congestive heart failure occurred are analyzed further (table 4). Mention already has been made of the fact that the incidence of congestive failure increased with the intensity of emphysema. It may now be pointed out that congestive heart failure in these cases represented primarily a failure of the right ventricle, for in all these cases there was moderate to marked, grade 2 to 3, hypertrophy of the right ventricle whereas the left ventricle was not enlarged in seven instances and was enlarged minimally or grade 1 in the remaining seven cases.

As mentioned in the foregoing, the degree of pulmonary arteriolar obliteration itself does not seem to influence greatly the amount of right ventricular enlargement, yet it is of interest to note that in the cases of congestive failure there were only three out of the 14 cases in which there was no appreciable reduction in the arteriolar lumen, whereas in eight of the 18 cases in which congestive failure did not occur there was no appreciable arteriolar obliteration. I feel that although in emphysema these arteriolar changes may not play a predominant rôle in the production of hypertension within the pulmonary circulation, they must aid to some extent in bringing about the ultimate failure of the heart.

Summary

An anatomic study was made of the heart and pulmonary arterial tree in 32 cases of essential emphysema. It was found that emphysema produced enlargement of the right ventricle in 75 per cent and resultant cardiac failure with decompensation in 44 per cent of the entire group. The severity of emphysema seemed to be closely correlated with the incidence of congestive heart failure as well as to the frequency and extent of right ventricular enlargement. Arteriosclerosis of the pulmonary arterial tree was noted to some degree in 80 per cent of the cases. Arteriosclerotic changes were noted most frequently in the arterioles, and narrowing of the arteriolar bed was found in 66 per cent of the total cases studied. The degree of obliteration of the arteriolar bed seemed to be influenced by the severity of emphysema, yet there was no direct correlation between the degree of arteriolar sclerosis and the degree of right ventricular enlargement, nor any relationship between the extent of these pulmonary arteriolar changes and the extent of arteriosclerotic changes in the coronary arteries or the aorta. It was concluded, therefore, that the arteriosclerotic changes of the pulmonary vessels in emphysema represent secondary manifestations of an existent hyperten-

sion within the pulmonary circuit which probably is produced by obstruction in the capillary bed. Whereas it is reasonable to assume that when the degree of obstruction in the arteriolar system is great there is an augmentation of the pulmonary hypertension, it is doubtful that the amount of pulmonary arteriosclerosis seen in the usual case of emphysema produces alone a very marked obstruction to the pulmonary circulation.

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THE DIAGNOSTIC VALUE OF REGRESSION OF SECONDARY SEXUAL CHARACTERISTICS IN CASES OF HEMOCHROMATOSIS *

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CASE reports of hemochromatosis associated with regression of the secondary sexual characteristics have appeared in the literature sporadically.[1, 2, 3, 4] It is not generally appreciated, however, that these findings may appear relatively early in the course of the disease and, therefore, give a clue to the diagnosis before bronzing of the skin, enlargement of the liver, and diabetes become diagnostically manifest. The two cases herein reported are illustrative. The first case was studied before we were aware of the fact that signs of hypogonadism or anterior pituitary insufficiency occurred in conjunction with hemochromatosis. As there was comparatively little pigmentation present, the making of the diagnosis was difficult in the first case. In fact, the diagnosis was made somewhat accidentally and the possibility of hemochromatosis was not very seriously entertained before the results of biopsy of the skin were reported. In the second case, however, largely because of our experience with the first case, the possibility of hemochromatosis was immediately entertained even though there was very little pigmentation present and the urine contained no sugar.

CASE REPORTS

Case 1. A man, aged 47 years, a railway brakeman who was not addicted to the use of alcohol, registered at the clinic in November 1929. Six months previously, symptoms of diabetes mellitus had appeared, and two months later sugar was found in the urine. The blood pressure was 120 mm. of mercury systolic and 84 mm. diastolic. The edge of the liver was palpable 3 cm. below the right costal margin anteriorly, but otherwise his examination disclosed nothing of consequence except a partial *nasal* hemianopsia of the right eye. As the result of treatment with insulin, his health improved so that for the next seven years he was able to work at his occupation.

In January 1936, the right hand became infected. Shortly thereafter his abdomen began to enlarge because of ascites. Periodic removal of the fluid by paracentesis became necessary. On April 6, 1936, the patient again reported at the clinic for examination. It was found that he was 5 feet 10 inches (175 cm.) in height and weighed 123 pounds (55.9 kg.). He was decidedly emaciated. The skin was dry and sallow. There was a suggestion of generalized pigmentation and there was considerable pigmentation over the shin bones, but the pigmentation was not as noticeable as the accompanying photograph (figures 1 and 2) would indicate.‡ The beard

* Received for publication May 9, 1940.

† Now residing in Chicago, Illinois.

‡ Possibly the pigmentation would have been more noticeable had he not been occupying a room with an individual who was intensely pigmented and who was suspected of having, but did not have, hemochromatosis.

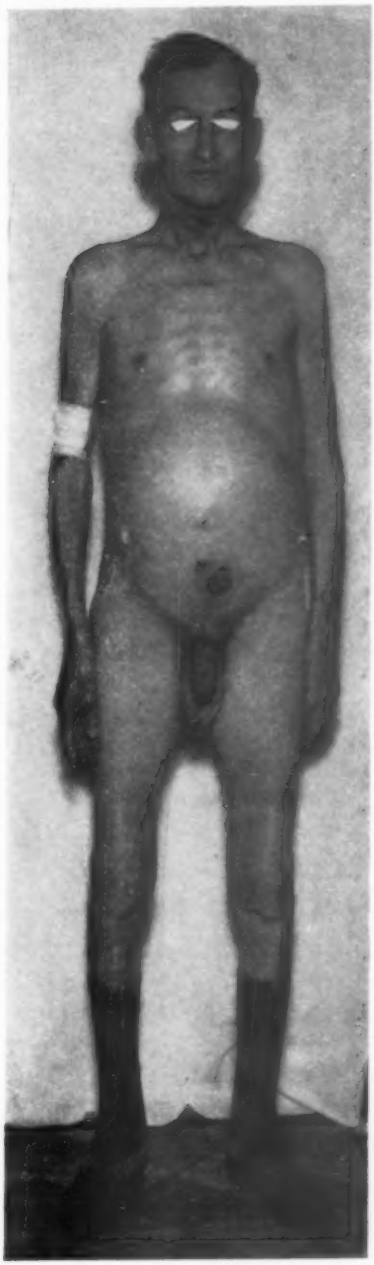

FIG. 1. Appearance of patient on admission to the hospital. Note the scanty pubic hair. The face, hands, and neck appear more pigmented than they actually were. Compare with figure 2.

seemed to be normal but the cutaneous hair elsewhere was very scanty. The axillary and pubic hair was diminished and the latter was feminine in its distribution. Free fluid was demonstrated in the abdomen. The liver was enlarged and readily palpable about 8 cm. below the costal margin, but the spleen could not be felt. The edge of the liver was thickened and rounded. One hemorrhage was found in the retina of

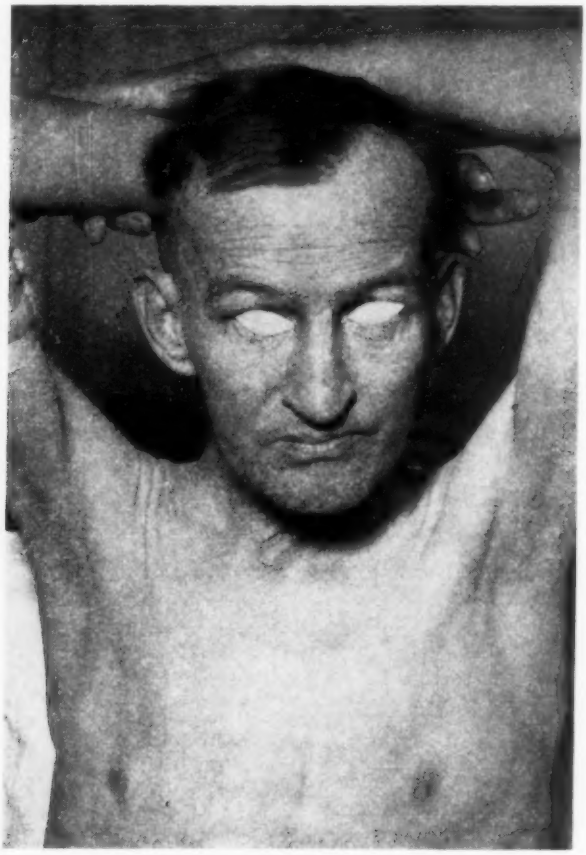

FIG. 2. Note the scanty axillary hair, and the absence of hair on the chest and around the nipples.

the right eye. The retinal arteries were slightly narrowed and there was some pallor of the right optic nerve head. The nasal hemianopsia was again noted. The blood pressure, in millimeters of mercury, varied from 120 to 140 systolic and from 70 to 80 diastolic.

In brief, the appearance of the patient was not greatly unlike that which occurs in cases of Simmonds' cachexia, except for the fact that ascites and hepatomegalia were present.

Although the laboratory studies (table 1) resulted in diagnoses of diabetes mellitus, probable cirrhosis of the liver, nephritis (type undetermined) and coronary sclerosis, we nevertheless had the impression that there was an additional pathologic factor present. Mainly because the liver was enlarged, a biopsy of the skin was performed. Somewhat to our surprise the skin showed the changes unquestionably diagnostic of hemochromatosis.

TABLE I

Special and Laboratory Studies

Urine	Blood
Specific gravity, 1.010–1.015	Hemoglobin, 11.1 gm.
Albumin, grade 3	Erythrocytes, 3,580,000 to 4,380,000
Pus, grade 1 to 3	Leukocytes, 6,900
Erythrocytes, grade 1 to 3	Differential count:
Sugar, 0 to 21 gm.	Lymphocytes, 13.0 per cent
Acetone, occasionally present	Monocytes, 3.5 per cent
Urobilin, 0	Neutrophiles, 82.5 per cent
Urobilinogen, 0	Basophiles, 1.0 per cent
Hemosiderin, 0	Slight poikilocytosis and anisocytosis
Culture: *Escherichia coli* present	There was no evidence of macrocytosis
	Flocculation test for syphilis negative

Blood chemistry (in mg. per 100 c.c. unless otherwise specified)

Sugar, 112 to 345	Sulfates, 7.0 to 7.8
Carbon dioxide combining power, 46.6 vols. per cent	Sodium, 339 to 342
	Potassium, 25.3
Chlorides, 511 to 635 (as NaCl)	Serum protein, 6.8 gm.
Cholesterol, 264	Albumin-globulin ratio, 1.06:1
Calcium, 9.2	Serum bilirubin, 1.0
Phosphate, 4.8	Van den Bergh reaction, indirect
Phosphatase, 2.3 units	Urea, 39 to 76

Miscellaneous examinations

Roentgenograms of the head, sella turcica, and thorax: negative
Roentgenograms of the right leg: marked calcification of the arteries; dense osteitis of the anterior and lateral aspects of the midportion of the tibia
Intravenous urogram: renal function too poor to outline kidneys
Electrocardiogram: sinus tachycardia, iso-electric T-waves in derivation I, diphasic T-waves in derivations II and III
Paunz test for amyloid disease: negative
Liver function test (bromsulfalein method): no retention of dye
Urea clearance: 37.8 c.c., volume 180 c.c.
Sulfate clearance: 29.6
Examination of ascitic fluid—Pon's test for hemosiderin: negative
Basal metabolic rate: 0 to —5 per cent

With treatment, the condition of the patient improved. The diabetes presented no difficulties and was readily controlled by regular insulin (60 to 75 units) and by a diet containing 300 gm. of carbohydrate, 79 gm. of protein, and 100 gm. of fat. Shortly after the patient's admission to the hospital 4,500 c.c. of clear fluid were removed from the abdomen by paracentesis. Later, satisfactory diuresis could be maintained by administering orally 12 gm. of potassium nitrate or potassium chloride daily. The administration of either of these salts obviated tapping the abdomen and reduced the concentration of the blood urea. The patient was dismissed in relatively good condition. Three months later he died at home. As necropsy was not performed, we never learned the nature of the renal lesions. Renal insufficiency is an unusual complication of hemochromatosis, possibly because hemosiderin is deposited in the renal cells to a limited extent as compared with other parenchymatous organs.* Chronic pyelonephritis might easily have been the etiologic factor.

Case 2. A white man, aged 40 years, a University professor, came to the clinic August 2, 1939, because of fatigue and an ache low in the back. He had been married eight years and for the last six years he had been impotent. When coitus was possible there was no ejaculation. Previously, his health had been exceptionally good. He was not addicted to alcohol. He was unaware of any change in the color of his skin except what he could attribute to exposure to the sun.

* The case reported by Hurxthal is an exception to the rule.[5]

Physical examination revealed a slender, poorly developed man who was 5 feet 7 inches (167.5 cm.) in height and weighed 131 pounds (59.5 kg.). The hips were broad. His appearance was not unlike that of patients suffering from chromophobe tumor of the anterior pituitary body, and this possibility was immediately entertained. The skin, except for the exposed surfaces, was fine, somewhat waxy in color, and largely devoid of hair. The beard was sparse, the axillary hair absent, and the scanty pubic hair was distributed in typical feminine fashion. That portion of the skin which had been exposed to the light was slightly pigmented and there was some pigmentation of the creases of the palms, but there was no pigmentation of the buccal mucosa, lips, or gums. The liver was diffusely enlarged, firm, and easily palpable 4 cm. below the right costal margin, anteriorly. The spleen could not be felt. Both testes were small and atrophic. The blood pressure, in millimeters of mercury, was 106 systolic and 70 diastolic. Roentgenologic examination of the head, thorax, and spine disclosed no abnormal findings. The sella turcica was not enlarged. Erythrocytes numbered 4,750,000, leukocytes 4,800 per cubic millimeter. The content of the hemoglobin in the blood was 14.0 gm. per 100 c.c. The flocculation test for syphilis was negative. No retention of dye occurred with the bromsulfalein test for liver function. The serum bilirubin was found to be 1.3 mg. per 100 c.c. and the van den Bergh reaction was indirect. The basal metabolic rate was —3 per cent. A glucose tolerance test yielded the results shown in table 2.

TABLE II

Results of Glucose Tolerance Test

Time, hrs.	Blood sugar, mg. per 100 c.c.	Sugar in urine
*0 (fasting)	112	0
½	233	0
2	147	0
3	90	0

* One gram of glucose per kilogram of body weight was given.

Because of the enlarged liver and the signs of hypopituitarism and hypogonadism, a tentative diagnosis of hemochromatosis was made. The diagnosis was established by a biopsy of the skin which disclosed the typical deposits of hemosiderin around the sweat glands.

A diet containing liberal amounts of carbohydrate and treatment with testosterone propionate were advised. Three months later the patient suddenly died at home.

COMMENT

Hemochromatosis is a rare disease. It occurs chiefly but not exclusively among men. The etiology has never been determined. Possibly because of an inborn intracellular metabolic disturbance,* large amounts of hemosiderin, a pigment containing iron, become lodged within the cells of most of the organs of the body with the possible exception of the nervous system. The cells become so stuffed with pigment that degeneration or death of the

* For a detailed discussion of the entire subject the reader is referred to the very excellent monograph by Sheldon.[6]

cell, sometimes from rupture, occurs. The secreting cells of the glands of internal and external secretion, their connective tissue stroma, striated and cardiac muscle, the reticulo-endothelial system, the alveolar epithelium of the lungs, the cartilage and synovium of joints, and occasionally the walls of the blood vessels are the favorite sites for the pigment. In the adrenal glands a heavy deposit of hemosiderin may be found in the zona glomerulosa, but the remainder of the cortex and the medulla are unaffected. A marked deposit of pigment is found in the anterior pituitary body, particularly, according to Sheldon,[6] in the basophilic cells. The pars nervosa, like the adrenal medulla, escapes involvement. In the testes, the cells of the germinal epithelium become atrophic. There is little information regarding the condition of the interstitial cells. Curiously, to a large extent, the cells of the kidneys escape involvement. The same remark applies to smooth muscle.

Hemofuchsin, an iron-free pigment, is also deposited in some cells. On the whole, it is found most abundantly in those organs and cells that are least affected by hemosiderin, for example in smooth muscle. However, it also occurs in connective tissue and in the epithelial cells of the glandular organs. Histologically, the cells of the thyroid and parathyroid glands are found to be the sites of extensive pigmentation. In the skin there is not only a deposition of hemosiderin, especially in and around the sweat glands, but there is in addition a marked increase in melanin, the normal skin pigment, especially in the deep layers of the corium.

In addition to the histologic changes just mentioned, an extensive sclerosing process occurs in the thyroid gland, liver, pancreas, and spleen. This sclerosis is nonspecific in character and in the last three organs enumerated, it resembles the fibrosis that occurs in ordinary cases of cirrhosis of the liver.

From what has been said, it is evident that hemochromatosis affects the histologic structure of most of the cells of the body. What is truly remarkable is that the function of so many organs apparently is unaffected. For example, in our experience, even though the liver is extensively involved even to the point of producing ascites, hepatic function as measured by the elimination of bromsulfalein usually is not disturbed (case 1). The thyroid gland likewise apparently tolerates both the pigmentation and the fibrosis very well. In other words, myxedema * and parathyroid tetany as the result of hemochromatosis occur exceedingly rarely, if at all. To our knowledge there is only one case of hemochromatosis on record in which clinical evidence of adrenal cortical insufficiency has been demonstrated.[5]

The clinical features of the disease, namely cirrhosis of the liver, diabetes, pigmentation and sexual hypofunction, therefore, are readily explicable by the gross and histopathologic findings, namely sclerosis or pigmentation or both, of the liver, pancreas, anterior lobe of the pituitary, and

* In one of the cases studied by Butt and Wilder [7] at the clinic, the basal metabolic rate was —19 per cent but the clinical signs were not sufficiently definite to warrant a diagnosis of myxedema.

possibly the adrenal glands and testes. The pigmentation of the skin results from the increase of melanin and the deposition of hemosiderin and varies according to the relative amount of each present.

Fortunately, for clinical purposes, both hypogonadism and hypofunction of the anterior lobe of the pituitary body result in easily recognizable physical stigmas. In both of these conditions there occur a fairly characteristic pallor, loss of beard and of pubic and axillary hair, infantile genitalia and often distinctive changes in the habitus. It makes very little difference, for the time being, whether we regard these changes as evidence of hypogonadism secondary to deposits of pigments in the testes themselves or hypogonadism that in turn is the result of hypopituitarism. If any appreciable amount of diabetes coexists, as it did in case 1, current endocrinologic theory would favor the view that the testicular insufficiency is the direct result of the pathologic changes that occur in the testes.

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ANOREXIA NERVOSA *

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In 1868 Sir William Gull,[1] in an address at Oxford, first referred to a "peculiar form of disease occurring mostly in young women, and characterized by extreme emaciation." He presented a paper on the subject in 1874, in which he stated that the origin of the disease is "to be sought in the disturbance of the mind and a prolonged insufficiency of food and nothing more." Other writers described the condition,[2, 3] but Gull deserves credit for the name and the concept of the condition which is accepted at present.

There are several papers by the English writers [4, 5, 6, 7, 8, 9, 10] which deal with case presentations, and a very complete account is given by John A. Ryle.[11] Other English writers have described possible mechanisms involved in the production of the syndrome.[12, 13, 14]

The French have written vivid descriptions and have discussed etiologic factors.[15, 16, 17]

In this country there has been comparatively little material presented concerning this entity until the recent publications [18, 19, 20, 21, 22, 23] which report cases and consider differential diagnosis.

This paper is based on the study of 27 cases of anorexia nervosa.

Clinical Picture

The most striking single feature of anorexia nervosa is the extreme degree of emaciation present. It has been stated that the emaciation with marked retraction of the abdomen, sunken eyes and dilated pupils is comparable only to that of cancer of the esophagus. Important clinical features include: an abnormal psychic attitude, anorexia, amenorrhea or irregular scanty menses, weakness, and many varied gastrointestinal symptoms. The weight loss varies in accordance with the length of the illness and the acuteness of the anorexia. It is impressive that the patient may complain of little, and may even desire not to be treated, but may be brought in by concerned parents or relatives. Some of the patients complain of dryness of the skin and hair, brittleness of the nails, loss of libido sexualis, intolerance to cold, and appearance of premature aging.

The physical and laboratory findings include: lowered blood pressure, slow pulse, subnormal temperature, lowered basal metabolism, and sometimes alterations in the glucose tolerance curve. Roentgen examinations of the skull, chest, gastrointestinal and genitourinary tracts, visual field examinations, and the information gained by various special examinations add

* Received for publication November 27, 1939.

TABLE I

No.	Sex	Age	Height	Weight	Weight Loss	Duration	B.P.	Pulse	Temp.	Precipitating or psychic factor	Menses and duration of amenorrhea	Menarche Age
1.	F	24	67″	70 lb.	118 lb.	4 yrs.	115/80	80	98.2	Reducing diet	2 yrs.	14 yrs.
2.	F	24	61″	52 lb.	62 lb.	5 yrs.	98/70	76	96.0	Appendectomy	1 period per yr. for past 6 yrs.	16 yrs.
3.	F	34	60″	59 lb.	59 lb.	10 yrs.	100/84	72	98.4	Hysterectomy (ovaries not removed)	3 periods in 10 yrs.	14 yrs.
4.	F	17	64″	89 lb.	50 lb.	12 mos.	92/58	68	95.0	Quinsy and tonsillitis	1 year	11 yrs.
5.	F	20	61″	82 lb.	40 lb.	3 yrs.	105/80	58	99.0	Over-industry in college	3 yrs.	12 yrs.
6.	F	36	61¼″	94 lb.	40 lb.	6 mos.	122/70	64	98.0	Religious ?	Surgical menopause	?
7.	F	25	61″	75 lb.	40 lb.	12 mos.	86/70	44	98.0	Reducing diet	10 months	12 yrs.
8.	F	18	63″	86 lb.	40 lb.	16 mos.	106/54	58	96.4	Over-industry in school	2 yrs.	14 yrs.
9.	F	16	61″	92 lb.	40 lb.	12 mos.	80/50	42	97.0	Appendectomy	4 months	12 yrs.
10.	F	22	65½″	82 lb.	38 lb.	2 yrs.	94/60	60	98.0	Over-work away from home	18 months	14 yrs.
11.	F	19	67″	108 lb.	35 lb.	6 mos.	110/68	84	96.8	Unable to elicit	3 months	14 yrs.
12.	F	16	63″	78 lb.	32 lb.	12 mos.	90/45	60	96.0	Restricted diet to simulate a girl friend	10 months	13 yrs.
13.	M	27	65″	85 lb.	32 lb.	14 mos.	80/60	68	97.6	"Afraid to eat" because of G-I distress	Male patient	—
14.	F	20	62″	69 lb.	31 lb.	10 mos.	120/80	70	98.0	Hysterical attacks	2½ yrs.	15 yrs.
15.	F	18	63½″	50 lb. lowest 59 lb.	30 lb.	8 yrs.	66/?	62	97.2	Globus hystericus	Primary amenorrhea	—
16.	F	26	64″	93 lb.	27 lb.	2 yrs.	106/80	64	98.0	Not elicited	12 mos.	14 yrs.
17.	F	19	61″	79 lb.	26 lb.	15 mos.	90/50	43	98.0	Over-industry in school precipitated with commencement	Scanty	14 yrs.

TABLE I

Menarche Age	Bio-Assays: Friedman	Bio-Assays: Urinary estrogens and androgens	B.M.R.	Glucose tolerance	Weight gain	Period of follow-up	Response	Remarks
14 yrs.	Positive	10–20 R.U.	−32%	94–125–128–111–90–97	60 lbs.	2 yrs.	Good	Under intensive endocrine therapy and repeated treatment in hospital this patient's weight dropped to 70 lbs. A remarkable recovery followed forced tube feedings after all endocrine therapy was discontinued.
16 yrs.	Negative	Not done	−19%	95–179–154–160–102–77	31 lbs.	4 yrs.	Fair	There is a history of repeated hospitalizations and operations, and a psychiatric examination showed "a deep-seated neurologic defect."
14 yrs.	Positive	20–30 R.U.	−11%	94–208–224–319–313–178	14 lbs.	6 mos.	Fair	This patient made excellent response while hospitalized (gain of 14 lbs. in 15 days) but since returning home has not improved. Diet not continued.
11 yrs.	Positive	Less than 4 R.U.*	−42%	86–86–117–187–190–113	68 lbs.	5 yrs.	Good	Very little response to intensive endocrine therapy for a period of 3 years, then after stopping all therapy made a spontaneous recovery.
12 yrs.	Measurable prolan	Less than 4 R.U.*	−24%	65–109–165–117–61–60	48 lbs.	2 yrs.	Good	Given endocrine therapy while in hospital for a short time; after returning home and discontinuing her college education she recovered.
?	Not done	Not done	−15%	73–172–187–158–95–89	None	—	Died	This patient desired to return home where all attempts failed, although tube feedings were not tried; partial necropsy revealed no cause of death. The pituitary was not examined.
12 yrs.	Negative	Less than 4 R.U.*	−38%	84–113–113–109–98–80	14 lbs.	4 yrs.	Poor	Still maintains a highly neurotic temperament, often telephoning her physician to see if she should eat or not.
14 yrs.	Not done	Not done	Not done	62—2½ hrs. p. p.	46 lbs. (in 9 mos.)	8 yrs.	Good	After reassurance this patient returned to her home and gained 46 lbs. in 9 months.
12 yrs.	Not done	Less than 10 R.U.	−43%	88—3 hrs. p. p.	?	2 yrs.	Good	Obstinate constipation resulted in suggesting an operation for adhesions. Exploratory laparotomy only was followed by complete recovery.
14 yrs.	Measurable prolan	Less than 10 R.U.	−21%	4/27/38: 91–114–102–64–110–49 12/28/38: 97–152–136–126–51–79	40 lbs. (in 9 mos.)	1 yr.	Good	Thyroid was the only therapy aside from diet and the patient had taken only a total of 5½ grains when her first menstrual period returned.
14 yrs.	Negative	Less than 10 R.U.	−26%	73–120–178–160–160–127	None	4 mos.	Poor	A follow-up letter from this patient reveals that her mental attitude has improved but she has little appetite and no weight gain as yet.
13 yrs.	Measurable prolan	10–20 R.U.	−24%	78–84–128–110–103–81	16 lbs.	2 yrs.	Fair	Has not followed diet or rest as suggested, but mental attitude has improved. The death of this patient's mother during this period may be a factor in the slow progress.
—	Positive	Androgens 12 U.	−40%	78–87–103–89–90	7 lbs.	2 yrs.	Poor	No response to repeated reassurance and encouragement; this patient lives from charity funds and seems very well contented to remain ill.
15 yrs.	Not done	Not done	−13%	9/26/30: 74–134–180–153–138 1/10/39: 84–230–236–79–85–45	26 lbs. (in 6 mos.)	8 yrs.	Good	This case made a spontaneous recovery after she became interested in music.
—	Negative	Not done	−25%	56–104–111–105–84–70	None	—	Died	Fatal. This patient had intensive and energetic endocrine therapy for several months without improvement; tube feedings were started late in the course of her illness at home, but she just "faded away." Necropsy not done.
14 yrs.	Negative	30–40 R.U.	−23%	87–125–172–170–161–62	None	2 yrs.	Poor	There was an adequate trial on endocrine therapy without response. Attempt at recent follow-up has been unsuccessful.
14 yrs.	Negative	Not done	−20%	73—fasting	20 lbs.	2 mos.	Good	Good prompt response.

TABLE I (*continued*)

No.	Sex	Age	Height	Weight	Weight Loss	Duration	B.P.	Pulse	Temp.	Precipitating or psychic factor	Menses and duration of amenorrhea	Menarche Age
18.	F	25	59″	71 lb.	24 lb.	3 yrs.	90/60	76	98.0	Dysphagia (no organic basis for this)	3 yrs.	12 yrs.
19.	F	25	66″	96 lb.	24 lb.	2 yrs.	100/80	56	98.0	Marriage ?	Irregular and scanty	15 yrs.
20.	F	13	57″	63 lb.	22 lb.	6 wks.	90/50	68	96.0	Reducing weight (acute starvation)	2 mos.	12 yrs.
21.	F	30	60½″	88 lb.	22 lb.	12 mos.	98/60	68	96.8	Not elicited	Irregular 2 yrs.	14 yrs.
22.	F	29	61¾″	80 lb.	22 lb.	2 mos.	110/70	88	98.6	Disappointment in love affair—definite	Scanty—regular	13 yrs.
23.	F	21	65½″	88 lb.	20 lb.	10 mos.	95/60	56	98.0	Spontaneous abortion	10 mos.	14 yrs.
24.	F	17	62″	82 lb.	20 lb.	2 yrs.	75/60	64	94.2	Not elicited	12 mos.	15 yrs.
25.	F	27	65″	87 lb.	20 lb.	12 mos.	130/90	80	98.6	"Psychoneurotic type"	Surgical menopause at 18 yrs.	13 yrs.
26.	F	18	65″	83 lb.	20 lb.	2 yrs.	115/60	80	96.0	Incapability in high-school	Irregular and scanty	13 yrs.
27.	F	17	61¼″	90½ lb.	15 lb.	2 yrs.	100/60	44	97.0	Over-industry in school	17 mos.	14 yrs.

little to the clinical picture. In some cases the disturbed endocrine functions are especially interesting. Our findings in this respect will be discussed later. It frequently occurs, as it did in several of our own cases, that the condition is at first mistaken for Simmonds' disease and is separated from it with difficulty and often only after observation for some time.

ETIOLOGY

It is generally accepted that the background for this condition is a "morbid mental state," and Ryle [11] has pointed out the importance of searching for multiple contributing factors as to psychogenic cause. He states that "of all the diseases in which the adverse interactions of the mind and body play a part, anorexia nervosa is one of the most dramatic and significant. A psychic trauma or a foolish habit, or some combination of the two, results in a loss of appetite and a suppression of the menses. Starvation follows and with the starvation an aggravation of the anorexia. Faced with these symptoms and increased emaciation, domestic anxiety, and sometimes medical indecision still further complicating the situation, a young

TABLE I (*continued*)

Menarche Age	Bio-Assays: Friedman	Bio-Assays: Urinary estrogens and androgens	B.M.R.	Glucose tolerance	Weight gain	Period of follow-up	Response	Remarks
12 yrs.	Positive	Less than 4 R.U.	−21%	106–168–176–147–87–73	73 lbs. (in 3 yrs.)	5 yrs.	Good	This case had intensive endocrine therapy for a period of two years under observation here without any response; then after becoming interested in "Christian Science" made a complete recovery. At this time we have the patient on a mild reducing diet.
15 yrs.	Negative	Not done	−13%	92—3 hrs. p. p.	40 lbs.	2 yrs.	Good	No endocrine therapy was given in this instance, and the recovery has been satisfactory.
12 yrs.	Not done	Not done	−38%	107—fasting	40 lbs. (in 10 mos.)	6 yrs.	Good	Firm handling at home and dietary therapy alone accounted for this excellent response.
14 yrs.	Not done	Not done	− 8%	12/30/35: 94–176–187–118–80–45 1/16/36: 89–95–76–74–82–74	21 lbs.	7 yrs.	Fair	Following a trial on pituitary extract, antuitrin-S and insulin, dietary management alone has shown a fair response.
13 yrs.	Not done	Not done	−20%	105—fasting	15 lbs.	2 yrs.	Poor	This is a very unstable nervous type of individual, and there has been a poor response to repeated encouragement and reassurance.
14 yrs.	Positive	Less than 10 R.U.	−30%	8/25/37: 60–99–114–73–99–62 5/2/38: 73–98–107–104–51–59	20 lbs.	2 yrs.	Fair	Ovarian therapy with A. P. L. for a three-month period with coöperation in the diet accounted for this fair response.
15 yrs.	Not done	Not done	Not done	Not done	6 lbs.	5 mos.	Poor	No response to theelin, whole pit. extract, and antuitrin-S therapy.
13 yrs.	Negative	Not done	− 2%	82—4 hrs. p. p.	25 lbs.	2 yrs.	Fair	There is a gradual improvement in this case.
13 yrs.	Not done	Not done	Not done	80—2½ hrs. p. p.	13 lbs.	4 yrs.	Poor	This patient still has periodic episodes of "getting nervous and having vomiting spells and loss of appetite."
14 yrs.	Positive	10–20 R.U.	−27%	83–173–193–145–69–74	3½ lbs. (in 10 days)	—	Good	During 17 months of amenorrhea, various endocrine preparations were given without benefit. Under observation short time with increase in weight. No menses as yet.

*Estrogen assays done by the method of Kurzrok.[37] The others were done by Cuyler's method.[31]

woman, recently healthy and happy begins to cause alarm and to look 'like a victim of a famine privation.'"

One or more factors may be important in the precipitation of the syndrome among which may be: a congenitally inadequate nervous constitution, the additional nervous instability of adolescence, injudicious and radical reducing diets, loss of appetite following illness or surgical operation, hysterical self-inflicted starvation to attract attention or sympathy, psychic trauma from such causes as disappointment in love or marriage, death of a friend or relative, over-industry in school or college, fear of eating arising from manifestations of functional nervous disturbances of the gastro-intestinal tract such as hysterical dysphagia and functional indigestion. Fear of being thrust out of a sphere of protection formed by the illness may form the greatest obstacle to recovery. Sheldon[12] has advanced the belief that some cases have a pituitary abnormality and that there is a "special body-mind type" which is peculiarly apt to develop anorexia nervosa in response to emotional difficulty.

Table 1 is a summary of the findings in 27 cases of anorexia nervosa.

Symptomatology

A. *Anorexia.* The anorexia in these cases may be described as a loss of appetite and hunger amounting to a disgust for food. Everyone readily admits a large psychic element in nutrition. The situation is well stated by Keeton [24]: "the vegetative mechanism is constantly subjected to reflexes originating in the mental fields, if these are pleasurable there is a facilitation of digestion, if they are not there is an inhibition. A disturbing bit of news is received and the individual loses his appetite, if the adjustment is difficult he may become nauseated and vomit. One has only to look at the nervous worried patients who are suffering from anxiety neuroses to realize the great blockade that the mind offers in these patients to maintenance of a normal nutritional state."

Surmont [16] states that he found achlorhydria present in the type of person who is subject to anorexia nervosa. Berkman [18] reported a tendency to hypoacidity in his series of cases. There were 12 cases in our series that had Ewald test meals; achlorhydria was present in only one.

Our results were as follows:

Number of cases:	Degree of Free Acid:
1	No free acid
3	Below 20 degrees
3	Between 20 and 40 degrees
5	Above 40 degrees

Achlorhydria, therefore, is not a factor of importance in causing the anorexia in these cases.

B. *Loss of Weight, Emaciation, and Effects of Weight Loss.* One of the basic abnormalities in this disease is the failure of the patient to accept an adequate diet. As soon as there is insufficient food for body processes the tissues are utilized, and this produces weight loss. To protect these tissues when the intake is lowered the basal metabolism becomes depressed. In starvation, the carbohydrate stored as glycogen and the so-called "deposit protein" are oxidized first, later the body fat is drawn upon, and finally the body protein. The tissues of greatest physiologic importance are spared as long as possible. When the most vital organs are sapped, death results.

One of the most instructive accounts of the effect of starvation on oxygen metabolism is that given by Benedict [26] in his studies on a group of students:

"A group of 12 athletic young men, who were on diets of 3200 and 3600 net calories per day, were placed on a diet of 1400 calories for three weeks without changing their mental or physical activities. After the average weight had fallen 12 per cent below its original level, it was found that they were able to maintain this weight on a diet of 1950 calories, a little more than half of the amount originally required. Meanwhile the heat production during sleep had fallen to about three-fourths of its original value,

FIG. 1. *Case 2.* Age 24 years, height 61 inches, weight 65 pounds, weight loss 62 pounds in 5 years.

and the heat production per kilogram of body weight and per square meter of body surface was about 18 per cent lower than at the beginning of the study. The pulse rate was greatly lowered, some morning rates were reported as low as 33 per minute. Systolic and diastolic pressures were distinctly lowered, rectal temperature remained normal. There was a slight falling off in strength tests, but muscular efficiency did not seem to be impaired; in fact, actual measurements proved that on account of their lower weights they were able to walk a mile with less expenditure of energy than

at the beginning of the experiment. They lacked energy, they felt cold more keenly, and there was a marked diminution in sex expression coincident with reduced diet."

The above experiment demonstrates clearly the major effects of starvation, and emphasizes the fact that strength may be well maintained during

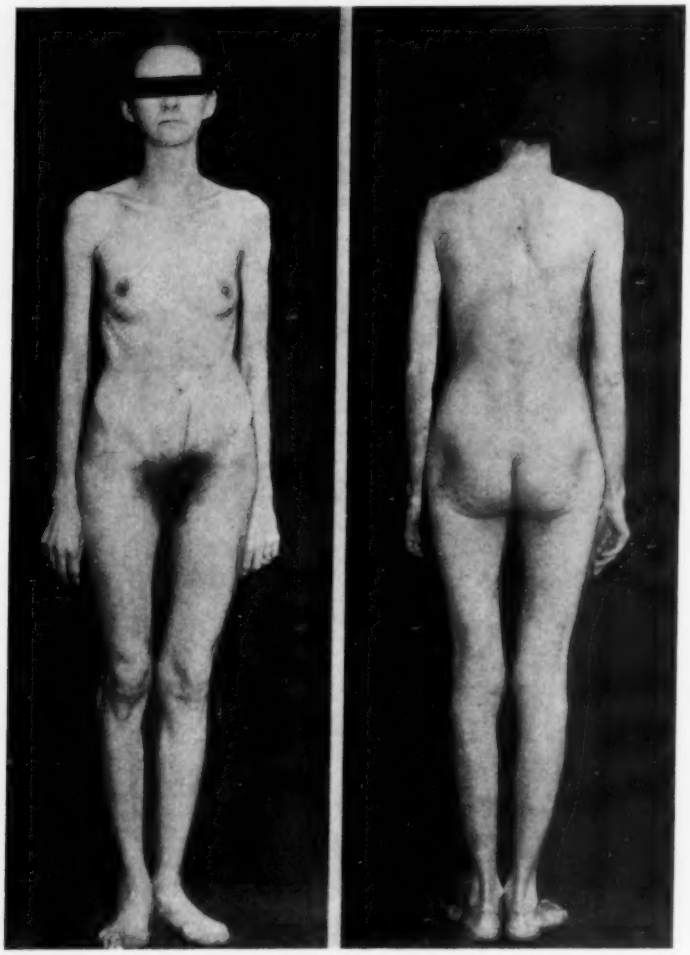


FIG. 2. *Case 2.* Five years later. Age 29 years, height 61 inches, weight 83 pounds. Note: The incisional scars present at this time resulted from an operation to "suspend the uterus" and two exploratory laparotomies for "abdominal adhesions."

considerable weight loss. Further effects of marked weight loss are marked weakness and inability to walk; and Keeton [24] has seen incontinence of urine and feces, suggesting the possibility of cord lesions. Such cases have been shown to be secondary to malnutrition, since the signs disappeared when food was administered.

Among our cases, two were fatal (cases 6 and 15); and in both in-

stances, although definite data are not available from the records, letters from the attending physicians indicated that they continued to lose weight and both lost more than half their body weight. In case 6 an incomplete autopsy was performed and no cause for death could be found. The adrenal glands were normal; the pituitary gland was not examined. There was no

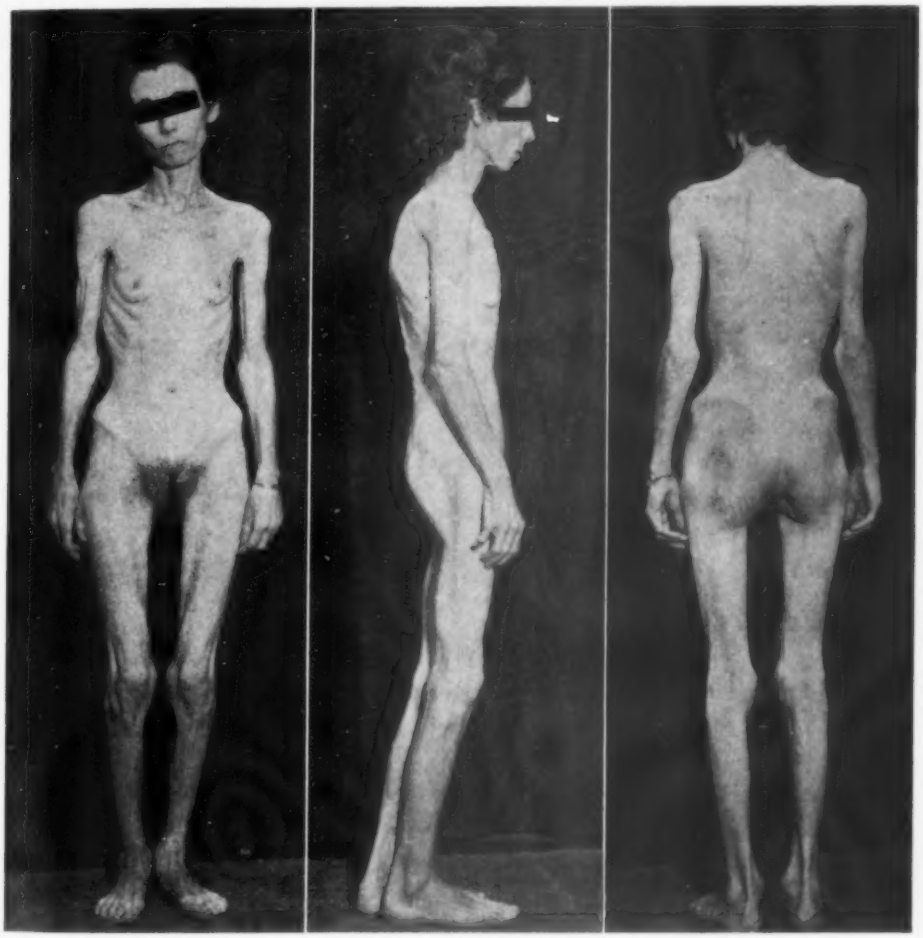


FIG. 3. *Case 3.* Age 34 years, height 60 inches, weight 59 pounds, weight loss 59 pounds in 10 years.

postmortem examination in the other fatal case. Usually if an individual loses more than one-half of the body weight the outcome is likely to be fatal. In one of our cases, body weight decreased from 188 to 70 pounds, following which the patient recovered and weighs 130 pounds at the time of this writing.

C. *Amenorrhea.* Amenorrhea is one of the cardinal symptoms in anorexia nervosa. Seventeen of our 27 cases had complete amenorrhea; five

cases had irregular and scanty periods; three cases had had operative interference previously; and in one case there were irregular and mildly profuse menstrual periods. The menarche was at 13 to 14 years in the majority of cases, the extremes being 11 to 16 years.

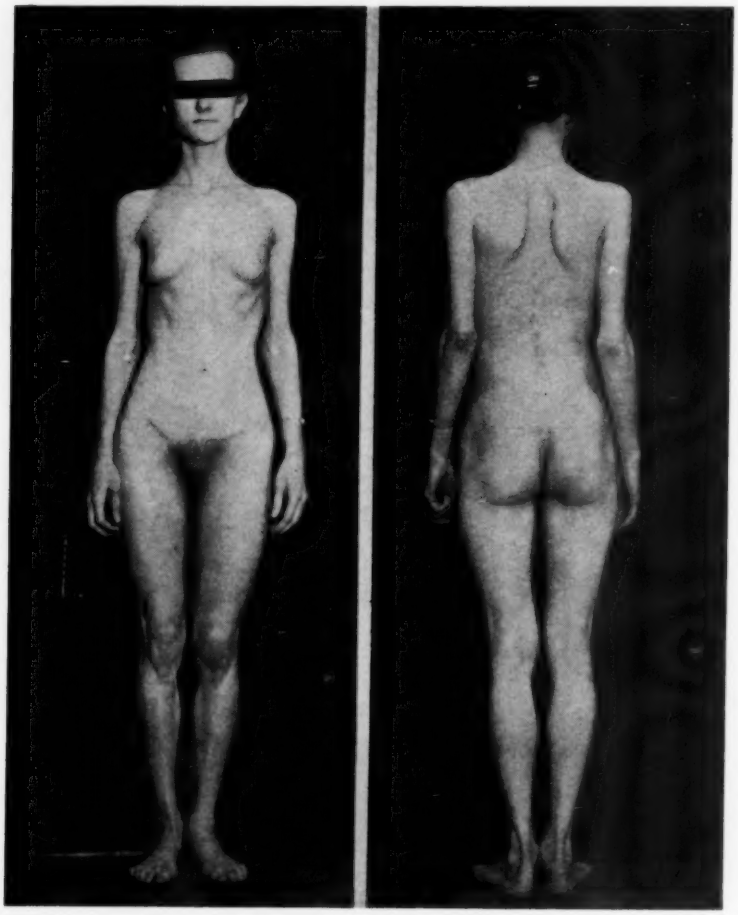


FIG. 4. *Case 10.* Age 22 years, height 65½ inches, weight 82 pounds, weight loss 38 pounds in 2 years.

With regard to the etiology of the amenorrhea, it appears that the starvation is the chief factor in most cases, as the amenorrhea usually follows considerable weight loss. The nervous or psychic factor, however, is apparently the major factor in some since the amenorrhea may precede weight loss as occurred in two of our cases. It appears to us that both factors are of importance. Whether the amenorrhea is psychic or nutritional, the mechanism must involve ovarian activity. Whether this is primary or pituitary in origin is not certain. Some of the hormonal studies appear to bear definitely on this point.

D. *Gastrointestinal Symptoms.* Apart from anorexia the most common symptom referable to the gastrointestinal tract is constipation, and this was practically a constant complaint in these cases. The second complaint in order of frequency was "gaseous dyspepsia" described as gas, bloating, feeling of pressure and fullness, all of which occurred after eating. Complete roentgen investigations of the gastrointestinal tract in 11 cases revealed no organic disease to account for the symptoms. Spasticity of the colon was present in the majority.

Physical Findings

A. *General Examination.* The most striking physical change was emaciation in the majority of cases. In addition, there was dryness of the skin, a senile appearance, and evidence of lowered metabolism. In only one case was there definite failure in development of secondary sexual characteristics and that was a fatal case. In an additional six cases there was a decrease in size of the breasts, and the uterus was described as being slightly smaller than normal. In two of these cases modified Friedman tests [21] were done, and were negative. Case 17 was an example in which the breasts were prominent in spite of the obvious under-nutrition. Examination of the fundi oculi and visual fields in 11 cases revealed no evidence of pituitary disease.

None of our cases showed any of the common clinical signs of vitamin deficiency. This is in accord with the observations of others. Bruckner, Wies, and Lavietes [22] state that in complete starvation specific vitamin deficiencies have not been noted, probably because the reduced energy requirements are satisfied by body tissues which are complete foods. It is probable also that the low level of metabolism in anorexia nervosa diminishes the requirements for vitamins.

B. *Blood Pressure, Pulse, Temperature.* In reviewing the table one readily observes a general lowering of blood pressure levels. Pulse rates are slow and in some instances temperatures subnormal. These changes are consistent with an attempt on the part of the body to preserve itself by conserving the expenditure of energy.

Laboratory Examinations

A. *Blood.* There were 10 cases in the series in which the hemoglobin content of the blood was below 80 per cent. In some cases pallor of the patient was so pronounced as to suggest anemia of rather high grade, and in some of these anemia was diagnosed by the ophthalmologist because of the degree of pallor of the fundi oculi; yet blood counts in the same individuals approached normal or came within normal range.

The sedimentation rate was determined in many cases and in all was within normal limits.

In several cases considerable study was directed toward blood chemistry, especially in regard to sodium excretion and blood levels of sodium, potassium, calcium, phosphorus, iodine, cholesterol, urea, and uric acid, but nothing of significance was encountered.

Repeated urinalyses were insignificant, and the blood Wassermann and Kahn tests were done in all and were negative in every instance.

B. *Basal Metabolic Determinations.* Twenty-four of the 27 cases had basal metabolic determinations, and the determinations recorded in the table were the lowest obtained during the period of observation. The number of cases within various levels were as follows:

Number of Cases	Range of B.M.R.
2	0 to —10%
5	—10 to —20%
10	—20 to —30%
4	—30 to —40%
3	—40 to —43%

Benedict [26] presented studies made in regard to the basal metabolism as affected by starvation in his subject, Levanzin, whose basal metabolic rate after 21 days of fasting fell to —30 per cent. Lusk [27] calculated that the fall in metabolism in this subject was caused not only by the decreased body and protoplasmic mass, but also by some specific and unknown factor which tends to protect the organism from the evil results of starvation. This protective mechanism offered by the body explains why the patients with anorexia nervosa have continued to survive on very low caloric diets. Other writers have reported very low basal metabolic rates in cases of anorexia nervosa, and the lowest basal rate that we have found recorded was that quoted by Sheldon [12] in Wittkower's case, in which the rate was —76 per cent.

Joslin [28] has done a total of 661 basal metabolism tests on a series of 113 cases of diabetes mellitus, and in a group of 20 cases with extreme loss of 35 per cent of body weight, the metabolic rates fell an average of 25 per cent (a loss of 0.63 per cent in metabolism for 1 per cent body weight). He contrasts this with the students studied by Benedict, who lost only 10.5 per cent in weight, with an average fall in metabolism of 19 per cent (a fall in metabolism of 1.8 per cent for each 1 per cent body weight). Joslin believes that this difference is due to the fact that normal men have a quicker loss and a quicker adaptability. It is interesting to note that the lowest basal rates in diabetics were found in girls from 16 to 18 years of age, one of whom gave a reading of —48 per cent, and this age is very common for the onset of anorexia nervosa.

C. *Glucose Tolerance.* The glucose tolerance was determined in 18 cases of this series. The method used was as follows: One hundred grams of glucose in water were given orally. Venous blood and urine specimens for glucose determinations were collected fasting and at one-half, one, two,

three and four hour intervals, the blood sugar being determined by a modification of the Myers-Bailey method.

In our patients we found the abnormal tolerance curves to be of two types: (a) decreased tolerance or a diabetic type of curve, in which the second and third hour determinations are high. The curve does not drop

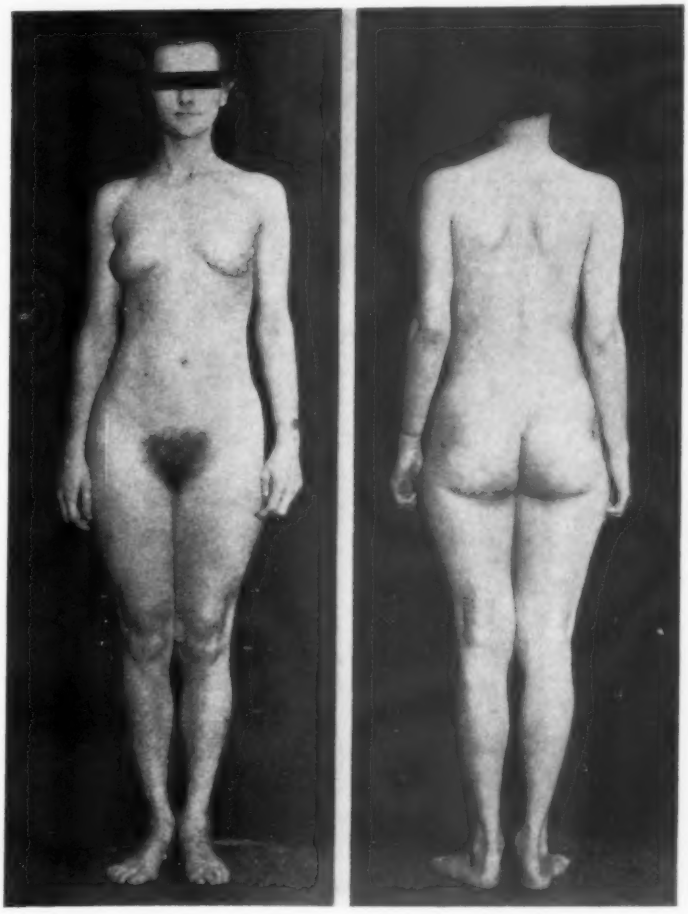
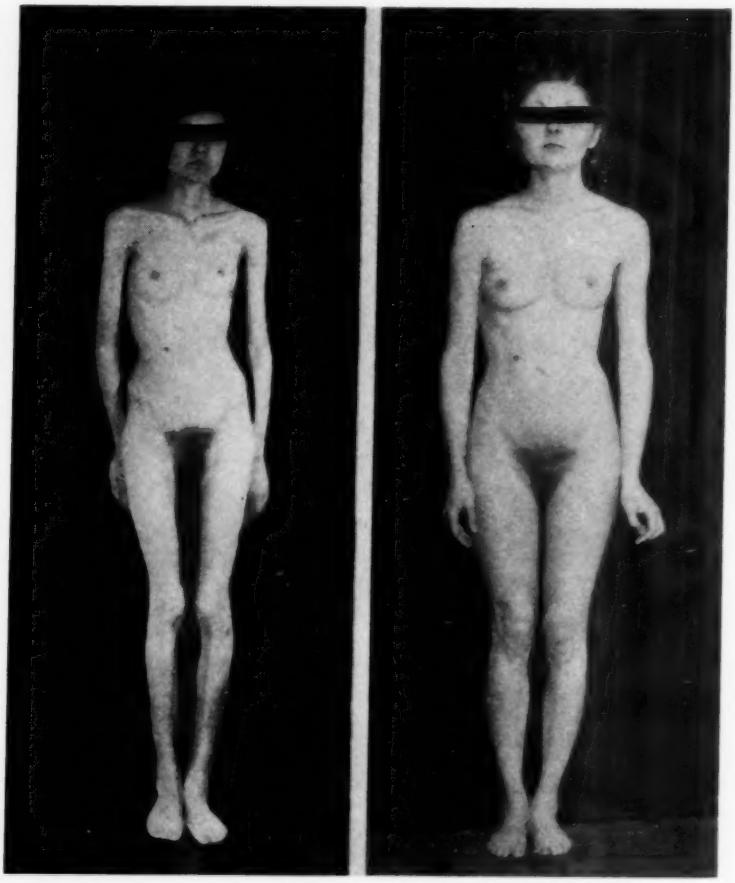


FIG. 5. *Case 10.* Fourteen months later. Height 65½ inches, weight 122 pounds.

to within normal limits completely at the fourth hour in some instances; and (b) increased tolerance or the low flat curve. This is the type of curve which has usually been referred to as a characteristic finding in pituitary cachexia. There were eight cases that revealed an increased tolerance, while four cases showed a distinctly decreased tolerance. In case 3 it will be noted that the curve is typically diabetic, and it is interesting to note that after following a high carbohydrate intake and a total of 3,000 calories daily

intake for 12 days, this patient had a normal blood sugar level two and one-half hours post prandial, and glycosuria had disappeared.

Previously a great deal of significance has been attached to the low flat tolerance curves as pointing towards the diagnosis of Simmonds' disease. It has been reported by us [29] and others that the glucose tolerance is very



a *b*

FIG. 6. (*a*) Age 20 years, height 62 inches, weight 69 pounds. Weight loss 31 pounds in 10 months. (*b*) Nine years later. Height 62 inches, weight 95 pounds (gained in 6 months).

definitely altered by the dietary intake in cases of diabetes and in functional hypoglycemia. In such patients on maintenance diets we found that the tolerance can be increased by increasing the carbohydrate intake and decreased by decreasing it as judged by repeated tolerance tests. The same type of change apparently occurs in some cases of anorexia nervosa as illustrated by case 14. Sweeney [30] has shown definite changes in the tolerance

curves following rigid dietary management for only two days in normal subjects. Sheldon [13] has recently discounted the significance that he had formerly attached to the flat type of tolerance curve seen in some of his cases of anorexia nervosa, and has reported a case of anorexia nervosa in which he has manipulated the curve by dietary control alone. Ross [14] recently recorded his observations on a case of anorexia nervosa with special reference to carbohydrate metabolism, and he believes that some liver preparations which he used in his patient have some influence on the regulation of the carbohydrate metabolism of these patients. We believe that the significance of glucose tolerance curves must be measured in terms of the diet used habitually for days or weeks preceding the test, and it is likely that there are other factors which influence this determination that are as yet unrecognized. Recent work has been done in an effort to detect the relation of vitamin B_1 to carbohydrate metabolism, and may prove to be of some importance.

D. *Hormonal Assays.* The gonadotropic hormone assays in this series were determined by a modification of the Friedman test,[31] which method gives a roughly quantitative determination. Assays for urinary estrogens were done by a method described by Cuyler,[32] except cases 4, 5, 7, and 18 which were done by the Kurzrok method.[37] The normal levels of urinary estrogens excreted in 24 hours vary usually from 20 to 50 rat units daily as estimated by the first method, 4 to 19 units by the second. Urinary androgen assays were done according to the modified Gallagher and Koch method as described by McCullagh and McLin,[33] the normal value for which is 18 to 80 international units per 24 hours.

The results of the bio-assays done are given in the table. It is not surprising that bio-assays in these individuals should show very low titers for estrogens since amenorrhea is so common. In 13 cases urinary estrogen levels were determined and only two approached average normal levels, whereas 11 cases showed a very definite decrease in the estrogen excretion.

It appears significant that among 18 cases in which qualitative gonadotropic hormone assays were done, an excess of this material was shown very definitely in seven cases, and a measurable amount was present in three. This seems to us to be very strong evidence against pituitary insufficiency as a cause of the symptoms, and appears to be a finding quite inconsistent with pituitary gland failure of an extent capable of producing pituitary cachexia. These findings strongly suggest the fact that the nutritional disturbance affects the ovaries directly rather than through the medium of the pituitary, and that the prolan excess is an evidence of compensatory pituitary hyperactivity. The women having excessive urinary gonadotropic hormone are noted to be cases in which the amenorrhea is of long standing in each instance, which lends still further support to this view.

E. *Roentgen Examination.* There were no positive findings except spasticity of the colon obtained in any of the roentgen examinations of the

gastrointestinal tract. Chest films were made in 21 cases. Evidence of arrested pulmonary tuberculosis was found in only one case.

Roentgen examination of the skull in 15 cases showed no evidence of pituitary disease.

Differential Diagnosis

It is extremely difficult and often impossible to differentiate anorexia nervosa and pituitary cachexia during life. Some similarities and differences in these conditions are mentioned below and other conditions more readily separated are discussed briefly.

(1) Simmonds' disease. The fatal syndrome of progressive weakness and cachexia, which was noted by Paulesco in 1907 following the removal of the pituitary gland, has been described in man prior to that date. It was not appreciated, however, that atrophy of the anterior lobe of the hypophysis was the primary etiologic factor until Simmonds called attention to it in 1914.[40] Pituitary cachexia is characterized clinically by: weakness, emaciation, falling of axillary and pubic hair, sensations of chilliness, gastrointestinal atony, atrophic changes in the skin, low blood pressure, low basal metabolism, and disturbance of the sexual functions including the cessation of menstruation, impotence and loss of libido. Pathologically, it is characterized by destruction of the anterior lobe of the pituitary gland, with secondary atrophic changes in the thyroid, parathyroids, suprarenal cortex, reproductive organs, and a decrease in the size of the abdominal organs (splanchnomikre). Various processes have been the cause of the destruction of the anterior lobe, including emboli, thromboses, tuberculosis, tumors and cysts, syphilis, and trauma. The diagnosis of Simmonds' disease is difficult, and we are inclined to agree with Silver [38] who thinks that it can be considered proved only when confirmed at necropsy. Proof of the diagnosis is nearly as complete, however, if it follows operative removal of a pituitary tumor and especially if, following such an operation, careful search at the time of operation fails to reveal any remaining pituitary gland.

The marked cachexia presented by the extreme cases of anorexia nervosa simulates Simmonds' disease very closely. In most instances it is possible to differentiate these conditions with a fair degree of accuracy after continued observation and study, especially regarding the course of the illness as influenced by attempted therapy. We attempt the differential diagnosis on the basis of the following:

DIFFERENTIAL DIAGNOSIS

Simmonds' Disease:	Anorexia Nervosa:
1. Age incidence: More common in adult women during child-bearing period.	1. Age incidence: More common in adolescents and between ages of 16 and 24 years.
2. History: Good health until onset; often history of puerperal sepsis, syphilis, trauma, or symptoms suggesting tumor.	2. History: Psychogenic background, and often a definite precipitating factor can be elicited.
3. Symptomatology: *a.* Weakness is pronounced. *b.* Anorexia is unassociated with neurotic trends. *c.* Digestive symptoms less marked. *d.* Amenorrhea usually is a matter of slight concern. *e.* Severe crises may occur causing death.	3. Symptomatology: *a.* Strength is surprisingly well preserved in spite of emaciation. *b.* Anorexia and emotional disturbances are intimately connected and a marked aversion to eating may be recognized. *c.* Functional indigestion is more prominent. *d.* The amenorrhea as well as other features may be matters of great alarm to the patient and relatives. *e.* If death occurs it follows typically, slowly progressive changes.
4. Physical signs: Definite failure in the secondary sex characteristics, atrophy of breasts, uterus, etc. Loss of axillary and pubic hair.	4. Physical signs: The breasts often escape the wasting until the final stages. Axillary and pubic hair are usually spared.
5. Neuropsychiatric: Dull appearance, poor memory, and intellectual impairment. In some cases spastic contractures of the limbs occur.	5. Neuropsychiatric: Usually impulsive; much more alert mentally; hysterical trends.
6. Laboratory evidence: *a.* Low B.M.R. *b.* Glucose tolerance increased as the rule. *c.* Roentgen evidence of erosion of the sella as seen in tumors, trauma, luetic lesions, etc., may be present. *d.* Visual fields—defects likely with tumor. *e.* Hormonal assays: 1. Gonadotropin assays—theoretically always very low. No measurable gonadotropin in one postoperative case studied by us. 2. Estrogen or androgen assays: Theoretically always decreased.	6. Laboratory evidence: *a.* Low B.M.R. *b.* Glucose tolerance may be increased or decreased. *c.* Roentgen evidence absent. *d.* Visual fields—normal. *e.* Hormonal assays: 1. Gonadotropin assays (Friedman test) may be positive or show measurable gonadotropin exceeding the normal. (However a negative test cannot be considered diagnostic). 2. Estrogen and androgen assays: Usually but not always decreased.
7. Course: Progressively downhill with lack of response to all endocrine therapy available at this time.	7. Course: Response to psychic and dietary therapy, and forced tube feedings if necessary.
8. Prognosis: Grave, though some cases live many years.	8. Prognosis: Dependent chiefly upon accurate diagnosis and energetic treatment.
9. Pathology: Almost complete destruction of the anterior lobe of the pituitary with secondary atrophic changes in other endocrine glands, viscera, and skin.	9. Pathology: All available data suggest that there are no characteristic changes in the endocrine glands or other organs.

(2) Addison's disease may be difficult to exclude at times, but the absence of pigmentation of the skin and mucous membranes, and a negative salt deprivation test with a high potassium intake, as suggested by Wilder et al.,[39] are good evidence against Addison's disease. Normal blood sodium and potassium levels are usually seen in anorexia nervosa, and there is no

marked improvement with large doses of sodium chloride and adrenal cortical hormone. In Simmonds' disease marked improvement may be observed under such treatment in some cases in crises.

(3) Intracranial lesions, such as neoplasm, will usually be accompanied by neurological findings as well as changes evident in skull roentgenograms or encephalograms.

(4) Malignancy. When malignant disease results in extreme emaciation it is usually associated with more marked anemia and a less striking fall in basal metabolism than is found in this condition. In most cases of advanced malignant disease clinical and adequate roentgen studies usually produce adequate evidence of its presence.

(5) Tuberculosis may be excluded on the bases of clinical, laboratory, and roentgen findings. There was one case in our series that apparently developed a mild tuberculosis probably secondary to malnutrition. This is apparently a rather common complication in anorexia nervosa. There was no evidence of tuberculous activity in any of our cases during the period of study recorded.

(6) Hypothyroidism may require consideration because of the existence of a very low basal metabolic rate. The hypometabolism in anorexia nervosa is due, we believe, entirely to starvation. In anorexia nervosa dryness of the skin and hair, and brittleness of the nails are common, as in hypothyroidism. Neither edema nor paresthesia was present in any of our cases of anorexia nervosa, whereas in cases of hypothyroidism with metabolic rates lower than minus 25 per cent, some evident edema about the eyes or hands is the rule. In anorexia nervosa the patients often appear to be very active mentally and physically, and their memory may be very accurate in contrast to the lowered mental vigor in thyroid deficiency. There is no marked tendency in hypothyroid states to the weight loss that is always prominent in anorexia nervosa; and finally, thyroid therapy is specific in hypothyroidism but produces little if any clinical improvement in anorexia nervosa.

Treatment

1. Reassurance and psychotherapy. The most important single phase of treatment is that of complete reassurance to the patient that organic disease is absent. A thorough examination is of considerable assistance in impressing the patient that organic causes have been excluded. Following this it is important that a definite diagnosis be reached. The patient and relatives should be impressed with the confidence of the physician in his own opinion. This establishment of complete confidence in the patient, explicit instructions, and firm handling are the most important features of successful management.

2. Diet. A high caloric and high vitamin diet should be insisted upon, and if necessary, tube feedings may be used in extreme cases. The use of a flexible latex tube containing a small bougie to maintain patency may be used,

and solutions of condensed milk will avoid clogging from milk curds. The fluid intake and deficient calories may be made up by the use of extra feedings or of glucose in saline intravenously.

3. Vitamins. We routinely add vitamin preparations by mouth, and more recently have been using crystalline vitamin B_1 preparations combined with liver extract as injections intramuscularly.

4. Endocrine preparations. In our cases there were many patients who were considered "pituitary failure" at the onset of the illness, and consequently many endocrine preparations, notably pituitary extracts, were given with the hope of favorable response. There were three cases in which continued and energetic use of many endocrine preparations resulted in continual downhill progression of the illness, and after discontinuance of this type of therapy and the instigation of forced dietary intake with added vitamins, we have observed favorable responses. There were a few cases that received endocrine preparations and maintained an adequate dietary intake at home that responded favorably, but in light of the failure in the other cases observed closely, we believe that dietary therapy was the cause for this response. With regard to thyroid, we consider the hypometabolism to be a compensatory and protective mechanism in most of these cases, and believe that thyroid is contraindicated where the weight is low since any increase in metabolism retards weight gain, which is of prime importance in the treatment. If hypometabolism remains after a normal weight is attained, and especially if amenorrhea still exists, the use of thyroid may be worthy of reconsideration.

Many of these cases show a rather definite sensitivity to insulin. If it is to be used, careful discrimination is advised. The response to insulin was of doubtful value in our cases and we feel that its value in this disease is decidedly limited.

In some of our cases the maintenance of normal weight and general good health for months has been associated with continued low urinary estrogens and persistent amenorrhea. In consideration of this we believe that some permanent damage to the ovaries may have occurred in some cases, particularly those of long-standing. In such instances gonadotropic or ovarian therapy is to be given serious consideration.

Prognosis

The earlier the diagnosis and the sooner appropriate treatment is arranged, the more favorable the prognosis. It is generally agreed that none of these cases is hopeless while life exists. In this series there were two fatalities, and in both instances it was impossible properly to control the patients and the dietary intake. Tuberculosis is a relatively common complication in cases of anorexia nervosa and with this added, the prognosis is grave.

Discussion

Many cases have been reported as Simmonds' disease in the literature with favorable responses to endocrine therapy. In the light of our experience of striking failure of response to available endocrine preparations over long periods of time, we believe that such cases usually represent, in reality, anorexia nervosa. Richardson [21] pointed out this likely possibility. In view of the greater likelihood of cases presenting themselves with this syndrome as caused by malnutrition than by having actual pathologic changes in the pituitary gland, we feel more caution should be exercised in making the diagnosis of pituitary cachexia.

Case 1 is a very good illustration of mismanagement of a case of anorexia nervosa. Here much dependence was placed upon endocrine therapy and adequate dietary intake was not forced. There may be other cases similarly mismanaged with fatal outcome, the fallacy being that while the attending physician is busying himself injudiciously in prescribing and depending upon endocrine therapy, he may accidentally overlook the real cure; namely, proper psychotherapy and the forcing of a high caloric intake.

In view of the very close similarity of anorexia nervosa and pituitary cachexia, the question arises as to whether dysfunction of the pituitary gland could be a reality and be secondary to nutritional factors. When general bodily nutrition is very poor all tissues must suffer to some degree and the glands are no exception. It is known that certain nutritional factors are of considerably greater importance than others in respect to pituitary activity. Experiments such as those of Parkes [34] indicate that such is the case. He showed that rats with normal estrous cycles became anestrous when fed a diet deficient in vitamin B. Transplantation of the pituitaries of such animals into young females indicated that the glands of the vitamin B deficient animals had less gonad-stimulating action than normal pituitaries.

The systematic investigation of the effects of dietary deficiencies on mammalian reproduction, and particularly on the estrous cycle was initiated by Evans and Bishop [35] (1922) with the aid of the vaginal smear technic. They showed that underfeeding of rats with an otherwise complete diet results in general aberration of the ovulation cycle; they further found disturbance of the cycle on unbalanced diets, and on diets deficient in salts. On diets deficient in vitamin A, rats showed abnormally prolonged estrous symptoms, whereas the absence of vitamin B resulted in a complete cessation of the estrous cycle.

More recently Barrie [36] has produced experimental evidence that suggests that vitamin E deficiency in rats causes failure of the normal reproductive process, of lactation, and of activity of the thyroid gland and that this is associated with deficiency in production of gonadotropic and thyrotropic hormones by the anterior lobe of the pituitary gland. This evidence was further substantiated by the histological findings. The conclusion drawn by Barrie is that vitamin E is necessary for the normal function of the anterior lobe of the pituitary gland.

It appears logical to suppose that in anorexia nervosa, where malnutrition plays the master rôle, there should be some effects from a lack of vitamins, and that lack of vitamins A, B, and E may contribute toward the development of the syndrome. The finding of large amounts of gonadotropic hormone in the urine in the presence of anorexia nervosa, however, appears to indicate that neither lack of vitamin B nor any other factor is causing pituitary sex hormone deficiency. If any specific nutritional factors are more intimately connected than others with gonadal deficiency, the effect would appear more direct upon the gonads and the excess of gonadotropic substances as shown by the Friedman test in our cases represents a compensatory pituitary hyperactivity. Until more definite knowledge is available, and especially since there is no obvious reason to believe that pituitary deficiency exists, it would seem wisest in the treatment of these cases to concentrate our attention upon the promotion of normal nutrition.

Summary and Conclusions

1. A brief summary of the literature and the findings in 27 cases of anorexia nervosa are presented.

2. The etiology, clinical picture, symptomatology, results of investigation, treatment, and prognosis are given with special emphasis on the similarity between anorexia nervosa and Simmonds' disease.

3. Concerning differential diagnosis, an important feature is the demonstration of an increased, gonadotropic hormone excretion in some cases of anorexia nervosa, a finding which is not consistent with severe pituitary failure.

4. It is suggested that vitamin deficiency may be a factor in producing the gonadal failure found in anorexia nervosa.

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EMOTIONS AND BODILY CHANGES; A REPORT OF SOME RECENT PSYCHOSOMATIC STUDIES *

By FLANDERS DUNBAR, M.D., Ph.D., Med.Sc.D., *New York, N. Y.*

A DISTINGUISHED member of this College made a statement some years ago which has served as both guide and inspiration to many of us who have turned our attention to problems of psychosomatic medicine. After it had been discovered what diverse illnesses might have an important source in emotional conflict, a controversy arose which reached its height a decade or so ago between proponents of psychogenesis versus physiogenesis of disease. It was against the background of this controversy that Dr. Walter B. Cannon made the comment

> An escape from the insistent demands of the pathologist for morphological evidence of disease, and also from the vagueness and mysticism of the psychological healers, can be found, I am convinced, in an understanding of the physiological processes which accompany profound emotional experience.

It was in these terms that we undertook to study in a general hospital † groups of patients suffering from different types of illness. After a preliminary review of cases showing combined medical and psychiatric problems it was decided that a better perspective would be obtained by studying serial admissions to the hospital in different disease groups whether or not any emotional problem appeared to be present. Over a period of ten years this investigation covered 1500 patients. These patients were observed simultaneously by way of the technics of physiology and clinical medicine, and the methods of medical psychology. The routine study of all admissions to the hospital for cardiovascular disease, diabetes, and fracture, as well as for some allergic and gastrointestinal disorders (in the age range 15 to 55) revealed an important psychic component in approximately 80 per cent ‡ of the patients who entered the hospital in a condition which made such study feasible.

Most estimates made by internists in this country, as well as by physicians operating under National Health Insurance in Great Britain, have given this figure as 34 to 40 per cent. But careful studies of industrial sickness

* Read at the Cleveland meeting of the American College of Physicians, April 5, 1940.

† In the department of medicine at Columbia University with the coöperation of the departments of psychiatry and surgery and aided by a grant from the Josiah Macy, Jr., Foundation.

‡ The 80 per cent of patients in whom this appeared to be the case were divided into the following groups:

1. Those in whom the psychic component was primarily a reaction to the illness itself—less than 5 per cent;
2. Those in whom it was a complicating factor affecting the course of illness and response to treatment—75 per cent;
3. (A subdivision of 2.) About 50 per cent in whom the psychic component was of *demonstrable* etiological significance in the development of illness.

and labor loss have brought out the important fact, that for every patient in whom nervousness or emotional conflict is readily obvious or elicited in the course of medical history and examination, there is at least one in whom it is extraordinarily well concealed. This is particularly likely to be the case when the patient has an actual somatic disorder. We ourselves were surprised in the early period of our study to find that more than half of the patients in whom we were able to demonstrate that the emotional component played a major rôle appeared both to themselves and to the attending physician to be completely normal happy human beings. Our own and other studies have called attention to the frequently inverse relationship of physiological and psychological symptomatology. For example, many of our "completely normal happy" people became neurotic when they were "cured" of their somatic disorder, and it was among this group that relapses were the most frequent.

Emotional Component in Patients with Cardiovascular Disease, Diabetes, Fracture

As will be seen from table 1 (which gives figures for three of the groups studied from July 1, 1934 to July 1, 1938) an average of 50 per cent of all the patients in these groups of serial admissions was found to be unsuitable for study on the basis of such factors as (*a*) death shortly after admission;

Table I

Patients in the Total Admission Groups Excluded from Detailed Investigation

	Cardiovascular Disease 1934–1938 out of 748	Diabetes 1934–1938 out of 148	Fractures 1934–1938 out of 232	TOTAL 1128
Reason for Exclusion:				
I. On the Basis of Illness or Defect:				
(*a*) Death shortly after admission	114	7	0	121
(*b*) Other primary complicating disease	164	20	17	201
(*c*) Psychosis	6	0	2	8
(*d*) Low mentality	17	1	7	25
II. On the Basis of Feasibility:				
(*a*) Referral elsewhere for chronic or terminal care	34	4	2	40
(*b*) For some reason not to be readmitted	9	2	1	12
(*c*) Transferred to the private service, referred to local physicians, or otherwise impossible to follow	66	21	49	136
(*d*) Language difficulties	16	1	3	20
Totals	426	56	81	563
Percentage of the total admissions both years excluded	(57.)	(38.)	(35.)	(50.)

(*b*) other primary complicating disease; (*c*) psychosis; (*d*) low mentality; or because referral elsewhere made adequate study impossible. It is of some interest that of the patients with cardiovascular disease, slightly more than half were excluded; of the patients with diabetes slightly more than a third; and of the patients with fractures about 38 per cent.

It is interesting with respect to the psychic component (table 2) that the percentages for the two-year periods charted are in such close accord.* It will be seen that the only significant difference in our figures for the second period of two years as compared with the first was in our estimate of the number of patients for whom psychotherapy was recommended. This is

TABLE II

	1934–1936 Per cent	1936–1938 Per cent	Four Year Period Per cent
OF THE PATIENTS SUITABLE FOR STUDY THE PSYCHIC FACTOR WAS			
Of significance in	79.	80.	79.
Inadequately determined in	21.	20.	21.
OF THE TOTAL PATIENTS ADEQUATELY STUDIED THE PSYCHIC FACTOR WAS			
Too much complicated somatically or too deep-lying for more than palliative treatment in	32.	8.	20.
Such as to warrant psychotherapy in	68.	92.	80.

accounted for in part by our omission during the second two years of all patients in the age group 50 to 55 among whom the suitability for study had been found to be much less than in the age group 15 to 50, and in part by our increased skill. We were surprised by the quick response of many of these patients to relatively superficial psychotherapy. Of course the question arises what were our *criteria* for judging whether or not the psychic component played an important rôle in the illness. Before giving these it may be useful to state a few points by way of amplification of the statement made at the outset concerning the perspective from which this study was undertaken.

Physiologists have shown that the bodily changes which are the most closely associated with emotional experience are the same changes that are the most immediate responses to other noxious agents such as bacteria or toxins, that is, changes in tension of smooth or striated muscle, changes in secretion (hyper- or hypo-secretion) and changes in circulation. It goes without saying that these changes may affect the function of any organ in the body, and of course if long persisting may be followed by secondary changes such for example as atrophy, or hypertrophy of the organ concerned.

* This was unexpected both because of the nature of the problems we were studying and because during the four-year period we were covering there were changes in our research staff involving study of patients by several different physicians with different training and personality. Tables 1 and 2 are reprinted with permission from the *American Journal of Psychiatry*.

Every physician in practice knows in general what is meant by these statements relative to bodily changes accompanying emotion but the subject has been made more concrete by recent psychosomatic studies; for example, by the research of investigators like H. S. Liddell who, following some clues provided by Pavlov was able to demonstrate similar phenomena in animals.

In Liddell's laboratory the following observations were made on animals which had been adjusted to laboratory conditions and trained in accordance with the conditioned reflex technic. It was found that if such an animal listens to a metronome and is fed when the metronome has a rate of 120, but at the rate of 50 is given no food, this animal readily learns to distinguish between the two and opens the food box only when the metronome has the proper rate. If then the rate of the slower metronome is increased to 80 or 100, so that it becomes difficult or impossible to distinguish between the two rates, many animals develop a constant state of tension. At the same time the heart rate increases, the heart may beat irregularly or develop extra systoles, and the animal shows similar disturbances in other bodily functions. The interesting thing is that after the animal has been subjected to the strain of attempting to make this discrimination it may no longer be able to distinguish between even a very slow and a very fast metronome. It seems to become worried; minor disturbances in the barnyard which never troubled it before become problems; it ceases to get along well with other sheep or pigs and is unable to relax at night. If then, such an animal is turned out to pasture and left alone with the others for a year or more the heart may quiet down, but animals were observed that when brought back to the laboratory in which this difficult problem was presented to them, at the first sound of the metronome or sometimes even on entering the laboratory, developed trembling, palpitation, and all the other physical disturbances experienced before. If you did not know, you would jump to the conclusion that they had been badly frightened there.*

Psychologists have been interested in the question: Under what circumstances may the normal physiological accompaniments of emotion become pathogenic? Relative to this point we have the following observations:

1. Such physiological changes may persist over a long period of time or become chronic when the associated emotion or conflict is inadequately discharged in appropriate action.

2. The associated emotion or conflict is particularly likely to be inadequately discharged if the individual has an inadequate appreciation of the problem with which he is faced, or is thwarted in solving it. (Under such circumstances he may even try to put the whole problem out of his mind and pretend it does not exist.)

This latter, of course, creates a problem in history taking. It has been said that every medical history of a patient contains three parts: what the

* One might wonder why the sheep was so disturbed by all this, why it did not simply open the food box whenever the metronome sounded knowing it would find food sooner or later. But this statement must be modified to the following extent: A sheep left free in the pasture and taught a maze with the finding of more food as a goal, when the problem becomes too difficult for it it simply lies down or grazes, showing no further interest. What makes the sheep susceptible to development of the neurotic type of behavior described when frustrated in its expectation or unable to distinguish metronome rates, seems to be the fact that it has already given up a good many degrees of freedom in its submission to the laboratory situation. This seems to have a bearing on neurotic types of behavior developed by human beings who have given up a good many degrees of freedom by submission to cultural patterns.

patient tells you, what the patient won't tell you, and what the patient can't tell you. It is this third part which is most important for psychosomatic diagnosis.

In our research, one of our major problems was the development of what we have called a psychosomatic history and of technics of eliciting such material. The first objective was to obtain a clear picture of the psychological as well as of the physiological make-up of the patient; the environmental stresses and emotional conflicts to which he had been exposed and his habitual manner of dealing with them. This latter is particularly important because as Sherrington has said, the most satisfactory release of instinctual tension is action, the least satisfactory is thought, and speech stands halfway in between.[1] There is a great difference between the people who on receiving "bad news" dash down to the ball field or to a movie, or to work, as compared with those who take time to go off by themselves and think it all over, or those who call in the neighbors or make a round of visits to their friends to tell them what has happened. The physiological accompaniments of the emotion aroused seem to be different in each case. In our observation, constitutional and other factors being equal, the patient with coronary disease or hypertension inclines to keep his feelings to himself and think whereas the patient with the accident habit has a long history of impulsive action under stress.

The following points were then evaluated as criteria of the significance of the emotional factor.

1. The emotional setting of early attacks as compared with attacks precipitated during interviews.
2. The appropriateness of physiological symptomatology (in terms of our knowledge of physiology) to the conflicts and emotional problems and character differences diagnosed.
3. The diagnostic opinion of five different observers as to the relative importance of the patient's psychic and somatic problems.
4. The patient's improvement or lack of improvement with therapeutic attention to the specific behavior pattern found to be characteristic of the disorder in question (see next section) without reference to modification of the external situation or the patient's total personality adjustment.
5. The patient's ability to stay well (as shown by follow-up visits) in spite of subsequent similar injury by the environment, whether through exposure to infection, or to mother-in-law or loss of job as the case might be.

In the course of this study, we became convinced of the truth of Sir William Osler's statement: that what happens to a patient with tuberculosis depends more on what he has in his head than what he has in his chest, and furthermore, that this statement applies equally well (with appropriate rephrasing) to patients with cardiovascular disease, diabetes, gastrointestinal disease, allergy or fracture. This is of considerable importance if we realize that the illnesses enumerated (with the addition of nervous diseases) account

for more than half of our total mortality and disability today. In other words, they make up the bulk of every physician's practice.

Correlations between Personality and Illness Syndrome

Even more interesting than the high percentage of patients in whom we found the emotional component in the illness important, however, were our observations concerning the types of persons that succumb to different types of illness. Of course we mean by this personality in terms of physical as well as psychological make-up. Patients in each of the disease groups studied showed fundamental similarities in the constellation, somatic make-up, major emotional conflicts, character resistances or characteristic ways of dealing with problems. They differed in these respects from patients in each other group studied although no factor was definitive.

Differences in this constellation seemed to be important:

First, because they were present in a high percentage of patients in each group in contrast to patients in other groups.

Second, because they could be shown to bear a close relation to the symptoms in question, often understandable in terms of physical changes accompanying emotion.

Third, because psychotherapeutic attention to them even without correction of other personality difficulties produced changes in the symptoms, first exacerbation when the material was brought up, and second relief as the material was worked through.

Fourth, because follow-up of patients with symptoms suggestive of certain of these illnesses and the related psychic problems has shown in some cases that the illness suggested by the symptoms had actually developed. This seemed to be particularly frequent where the psychic component of the illness was prominent and characteristic. Illustrative cases have been published elsewhere.[2]

Only a sketchy impression of these differences can be given but it is significant that many of them were differences that could be determined by any statistician who reviewed the medical charts. Their detection not only required no psychiatric training but also required little or no medical training. The differences under this category are differences in educational and occupational history, income, and early disease history. Although these points were checked only at the close of our study they are mentioned first because of their objectivity and because of their (to us, surprising) corroboration of our conclusions from the personality studies.

Chart 1, where each different shading represents a different disease group, shows the marked divergency of one group as compared with another. It may be interesting to note that our base line from which plus and minus deviations are determined represents the upper 60 per cent of the population. Using as a base line, educational averages for the total popula-

tion, all of our groups showed a positive deviation.* This offers some gauge of the selective factor brought in by the hospital itself. (In order to make our figures comparable with those for the total population which are

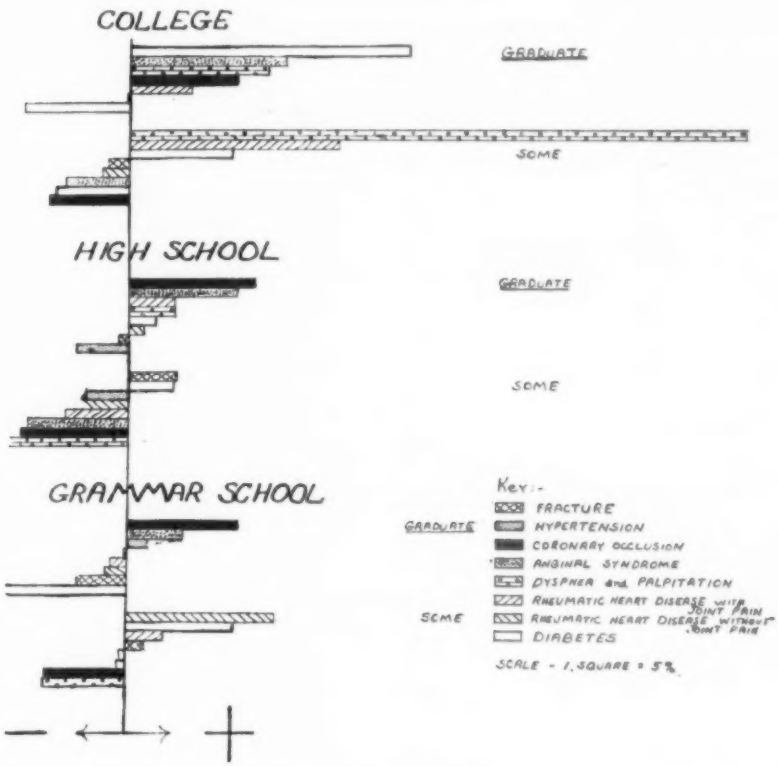

CHART 1. Educations.
Males—Females 21–55.
Base—Upper 60% General Population.

given in terms of persons over 21, we have charted only those of our patients who were over 21. But since all those over 55 are excluded we would expect a higher educational average than that for the general population because educational standards have been higher in the last 30 years than in the preceding 30 years.) We feel, however, that we have an adequate sample at least for our hospital because no significant change occurs in the deviations presented whether a series of 100 or of 150 patients is used for each group.

From this point on the discussion covers only three of the disease groups studied: patients with fracture, patients with coronary disease, and patients diagnosed anginal syndrome but without definite evidence of coronary occlusion. These groups included 430 of the 1500 patients in the total study.

* With the exception of the elementary school group where a minus deviation is really equivalent to a positive deviation in terms of educational level.

Chart 2 makes it possible to analyze the differences in educational history of the fracture group as compared with the coronary and anginal groups. All these groups have a higher educational average than that of the upper 60 per cent of our total population. Incidentally, the fracture

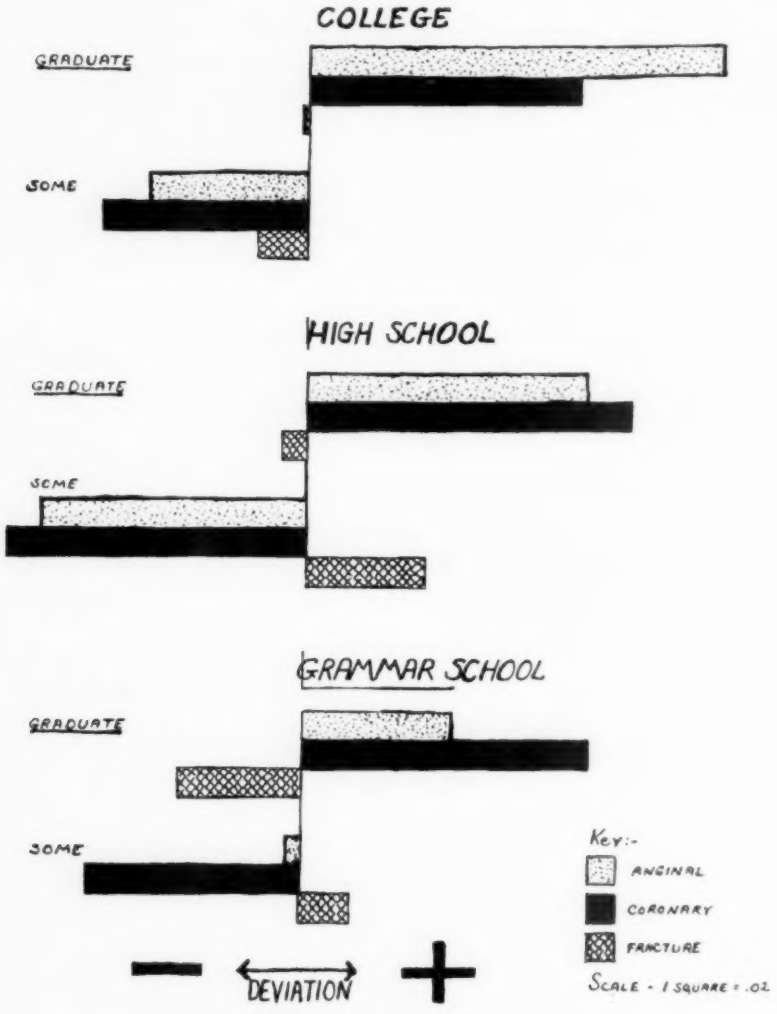

CHART 2. Educations.
Males—Females 21–55.
Base—Upper 60% General Population.

group pretty nearly represents the base line for the total number of patients covered in our study; most of the other groups shown on the preceding chart fall below them.

It may be noted that in the three categories representing termination of academic education in the middle of educational unit (that is some elemen-

tary school, some high school, or some college) the coronary and anginal patients show a minus deviation from the upper 60 per cent of the population, but that this is more than compensated by the marked plus deviation in *completion* of the educational unit in question or of a higher educational unit. The *fracture patients* on the other hand show a positive

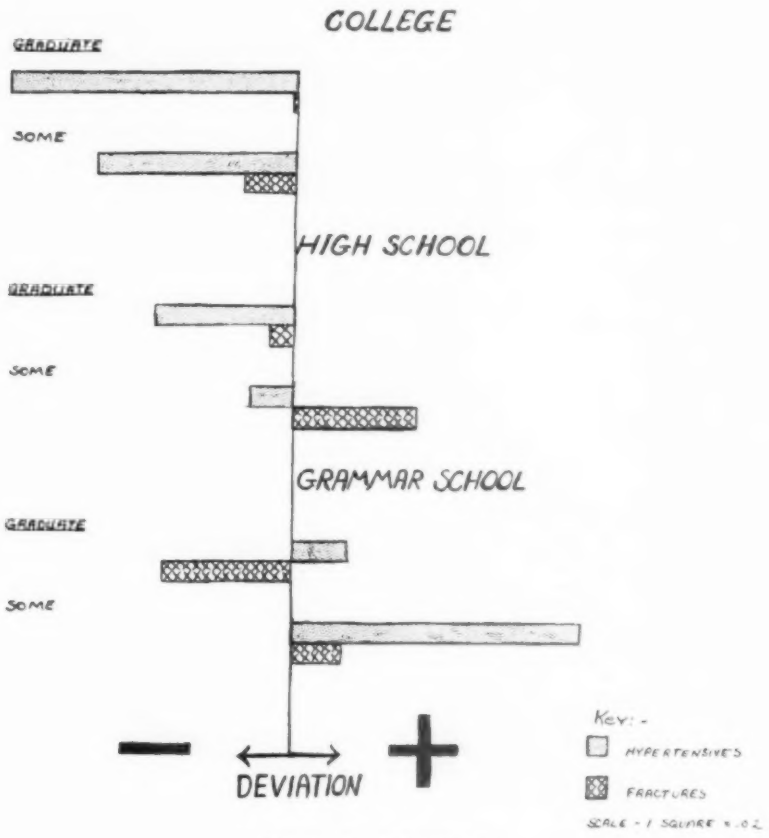

CHART 3. Educations.
Males—Females 21–55.
Base—Upper 60% General Population.

deviation from the upper 60 per cent of the population in the groups representing *incomplete* educational units (with the exception of the incomplete college group)* and a minus deviation in the groups representing completed educational units. As will be seen from chart 3 this does not mean that accident patients have a lower educational average than patients with cardiovascular disease: patients with hypertensive cardiovascular disease as well as other groups studied fell much below them, although in our series patients

* This minus deviation is probably to be explained in terms of the tendency of these patients not to go to college, plus other factors which in view of limitation of space cannot be discussed here.

with coronary occlusion and with the anginal syndrome without demonstrable coronary disease were markedly above them.

What is the bearing of these charts on the problems we are discussing? What is their significance for psychosomatic medicine? They interested us for the following reasons in terms of our personality studies of fracture patients and patients with coronary disease.

First, both groups were in conflict with authority and in both cases the onset of illness coincided with circumstances which made this conflict acute.

Second, these two groups of patients had completely different ways of dealing with authority; the former attempted to avoid any type of subjection to authority by becoming adventurers, by frequent changes of environment, occupation, boss and sometimes even wife; whereas the latter tended to stick to one job, usually their first job, for many years, working long hours without vacations until they themselves had become the authority. This tendency was borne out even by the history of marriage and divorce and size of family. Whereas about the same percentage of each group married, the average size of family for the coronary patients was much greater than that for the general population, whereas the average size of family in the fracture group fell far below the average for the general population. The educational charts indicate that this personality tendency toward self discipline and persistence among coronary patients and toward impulsive activity among fracture patients started early in life and was characteristic of the groups in question: the fracture patients had a tendency to leave school in the middle of an educational unit, and the coronary patients only after they had completed an educational unit. Typical case history excerpts are the following:

Fracture Patient: "I had always planned to study engineering. During my third year in High School I discovered that to do this I had to have two languages. This sort of discouraged me. It didn't seem worth bothering about at the time. So I left High School and joined the Navy. I didn't like the Navy but I didn't know just how to resign. Then I had an accident and got out. I worked in a boiler room for a while, then I joined the police force. That didn't go so well because I couldn't stand being bossed, it was just as bad as the Navy. And so, ever since then I've just done odd jobs."

Coronary Patient: "When I was twelve I ran away from home because I couldn't stand being bossed by father. I got a job as an errand boy in a butcher shop and finished High School at night. I worked up in the business until I was a clerk, a manager, and finally I was the boss of the business. I worked 14 to 18 hours a day and never took a vacation. But things went well and now I own a chain of butcher shops in the city."

In the fracture case the accident occurred while the patient who had been out of work for some months was looking for a job. "I was walking across the street with my hat pulled down over my eyes, thinking if I got turned down once more I could never go home and face my wife. I might as well sleep on a park bench."

In the coronary patient the onset of illness followed the acceptance of a partner in business "because it had become too much for one man to manage. But it always rankled because I wasn't my own boss anymore. My heart was heavy and I began to have pains."

It may seem absurd to cite such illustrations as these but to any practicing physician who has heard almost the same stories from one patient after another over a period of 10 years and stories which differ so markedly from one group to another they begin to assume significance. It may be amusing

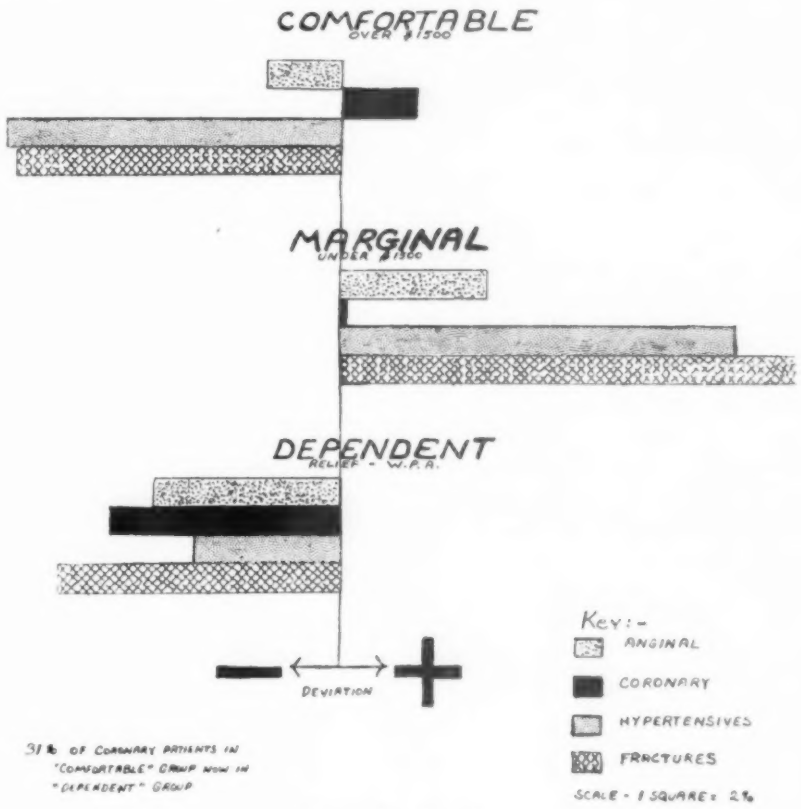

CHART 4. Incomes.
Males—Females 21–55
Base—General Population.

to note that when we first undertook this study although we were aware that a control group was out of the question and we could hope at best to study contrasts of one group with another, the fracture group was suggested to us as the most nearly normal group in the hospital because after all accidents happen by accident. At the time our study was undertaken, physicians under Health Insurance in Great Britain and Insurance Companies here were calling attention to the fact that only 10 to 15 per cent of accidents can be accounted for on the basis of defects in machinery, defects in skill, or physical or mental health of those involved. They were beginning to publish articles enquiring as to what this x factor in the personality was that predisposed certain persons and not others to accidents.[2]

When we first studied this question we found little that was significant in the situation preceding the accident in our patients. They were usually worried about a job, "a fight with the wife," being reproved by the priest, and so on. We thought at first that being out of work and having a low income might be a factor, but it is clear from chart 4 that the average income of these patients was above that of the patients with hypertensive cardiovascular disease. Actually it was above the average for the total number of patients studied.

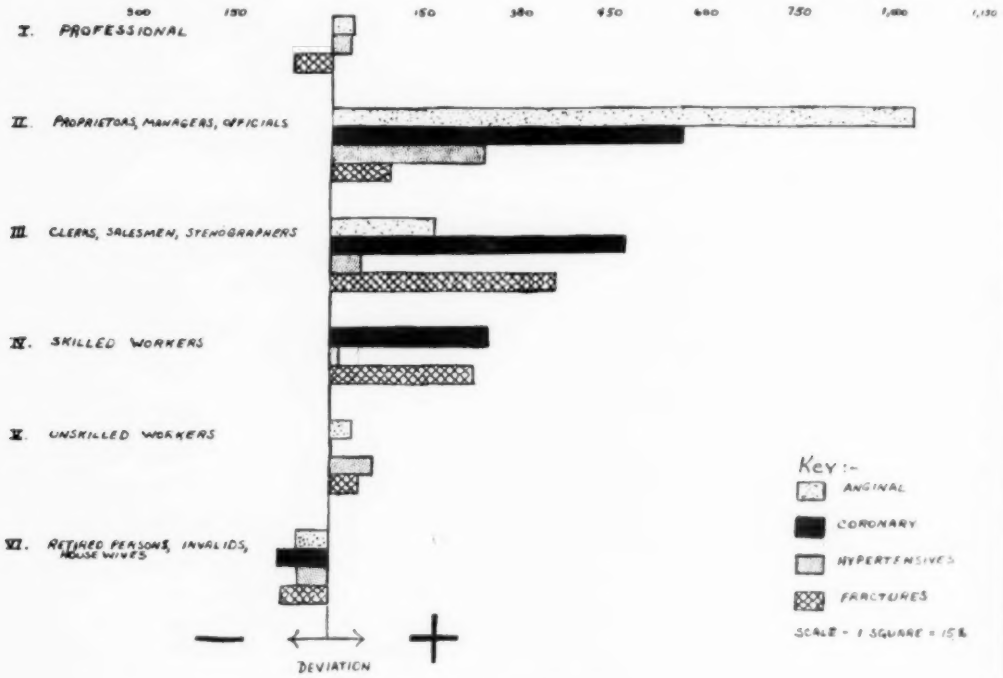

CHART 5. Occupations.
Males—Females 21–55
Base—General Population.

We thought that perhaps more of them were laborers and so more exposed to accidents. But we found more unskilled laborers among patients with hypertensive cardiovascular disease and more skilled laborers among patients with coronary disease, both of which groups have relatively low accident records. The percentage of "dangerous" jobs was as great among those who had coronary disease as among those who had accidents (see chart 5). These observations lend force to the characteristic of impulsive action under stress (and related patterns which cannot be given here) as a possible clue to the personality factor in accident proneness; in conjunction with the material to follow they suggest also that the opposite characteristic among patients with coronary disease may have a bearing on their illness, too.

A picture of the *illness history* prior to the development of the illness in question is perhaps the most interesting of all.

First, 72 per cent of the fracture patients had had one or more previous accidents.* Fifty per cent of them had had two or more, the maximum being 27, whereas only 2 per cent of the patients in the other groups had had more than one accident.

Second, apart from their accident history, the fracture group had an illness record which is in marked contrast to that of the other groups and

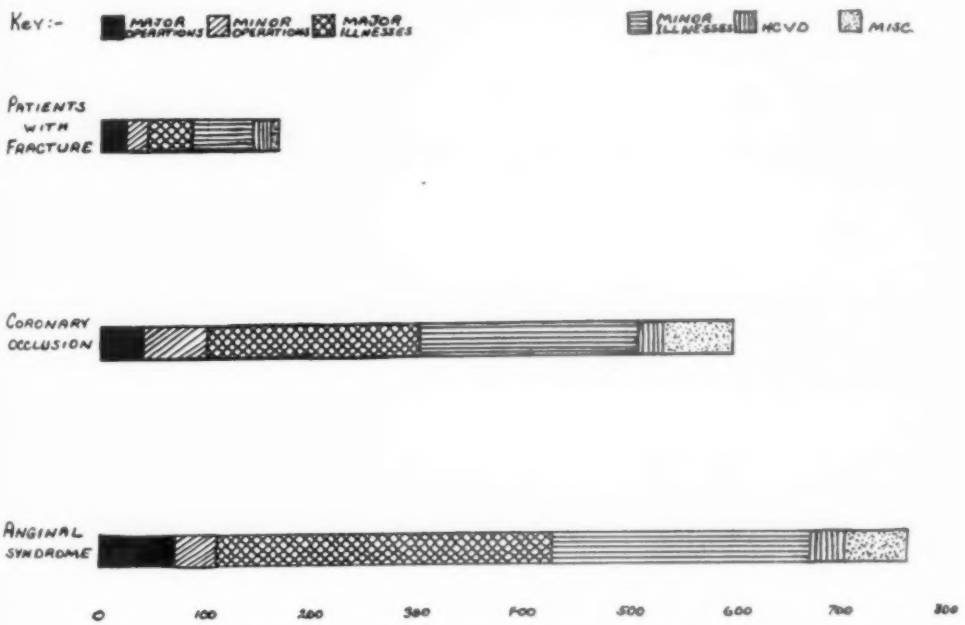

CHART 6. Illness incidence prior to present illness.
(Corrected for age and sex distribution.)

much better than that for the general population (see chart 6). The total previous illness history (excluding accidents in all groups) for coronary and anginal patients was about five times as great as that for the fracture patients even after the figures had been corrected for age distribution. The majority of them represented disorders involving vegetative functions such for example as gastric or duodenal ulcer, acute appendicitis, gall-bladder disease, genitourinary dysfunction or pathology. (See chart 6.)

And most interesting of all in spite of the points noted with regard to income and occupation, accidents represented only about 6 per cent of the illness history for the other two groups whereas they represented 76 per cent of the illness history of the fracture patients.

It will remain for future study to determine whether or not our sample was adequate, and to evaluate the selective factor brought in by our par-

* For fuller detail see references 3 and 4.

ticular hospital in terms of its geographical and metropolitan location, and the income group it serves. But, whatever later studies may show, it seems to us that these purely objective facts even aside from some very significant observations with regard to conflicts and behavior patterns in these patients indicate psychological and physiological (that is psychosomatic) differences between the disease groups studied. As already noted the charts relative to objective data were made only after we had reached certain conclusions from personality studies of these patients, and we ourselves were surprised to what a degree they were complementary and confirmatory.

Implications for Therapy

Although in the space allowed it is impossible to discuss therapy, it is easy to see that the accident patient with his tendency to avoid authority and responsibility is likely to become a difficult problem in the hospital especially if he is a compensation case, or if he feels guilty about this tendency to avoid or to act impulsively. The hospital gives him an excuse to be taken care of which he may be inclined to exploit. The coronary patient on the other hand may need to be encouraged to relax and allow himself to be taken care of, and to relinquish a little of his sense of responsibility.

Follow-up of the patients studied, covering a period of from two to ten years, showed a marked difference between patients treated by psychological methods in addition to the clinical routine, as compared with patients not so treated. This difference was in the main in the patients' ability to stay well even though exposed to all the same external difficulties. In the untreated group recurrences of the illness in question, and readmission for a new illness or accident occurred in the majority of cases. In the treated group readmission was rarely necessary. This subject together with statistics is discussed in another publication.[5] This observation seems important since the illnesses studied represent the major causes of disability and invalidism in our population today.

Conclusion

First, we have reported differences in personality, including differences in physiological and psychological behavior patterns in patients with different illnesses.

Second, these seem to have a bearing on the type of illness developed, although in the space allowed, this has not been adequately demonstrated.

Third, Sherrington's comment relative to expression of tension in action vs. expression in thought accompanied by vegetative changes seems to be borne out by the histories of the two groups of patients presented in detail. Similarly evidence is supplied for the laws of emotional economy variously stated by Dr. Adolf Meyer and Freud that emotion which is repressed does not become ineffective but has its effect by way of other channels often involving the vegetative functions.

Finally, we have added a little more factual background to the old medical axiom—"it is more important to know what kind of patient has a disease than what kind of disease a patient has."

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MUCOUS COLITIS: A DELINEATION OF THE SYNDROME WITH CERTAIN OBSERVATIONS ON ITS MECHANISM AND ON THE RÔLE OF EMOTIONAL TENSION AS A PRECIPITATING FACTOR*

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Mucous colitis is a bodily reaction rather than a disease entity. In this it resembles such syndromes as asthma and epilepsy. Its manifestations are manifold and inconstant, often overshadowed by other symptoms, sometimes adeptly mimicking unrelated disease. The clinical picture is a hazy one at best, yet because of the very qualities which characterize it, its recognition is extremely important. Mucous colitis is probably responsible for the removal of more undiseased appendices than any other one cause. It is often mistreated, with resultant invalidism which may in some instances be avoided. It accompanies many of the states of emotional tension which are encountered in practice. Its apparently close physiological relation to such tension suggested to the authors the value of a clinical and psychological review of the syndrome.

DaCosta [1] was the first modern clinician to present adequately the syndrome of mucous colitis. In his paper is to be found an excellent list of references to the classical literature and to the early nineteenth century contributions. No attempt is made here to review in detail the history of the syndrome, but in many of the subsequent paragraphs reference is made to the significant work published since the appearance of DaCosta's article.

During a period of two years an attempt was made to study all the cases of mucous colitis which could be found in the wards or out-patient department of the Massachusetts General Hospital. In addition to cases obviously recognized as mucous colitis the authors attempted to interview briefly all patients with unexplained diarrhea, abdominal pain, or symptoms of the anxiety state. In this way certain patients were located who would otherwise have been overlooked. Many of the patients so interviewed, of course, showed no confirmatory evidence of mucous colitis and were disregarded. A total of 60 patients was studied clinically in sufficient detail to afford a basis for certain statistical deductions. Of these, 57 were studied in a psychological manner with sufficient thoroughness to afford considerable insight not only into the rôle of precipitating emotional factors but also into the types of personality encountered in the victims of the syndrome. The present report is concerned primarily with the clinical findings.

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I. Clinical Syndrome

In general the symptoms and signs of mucous colitis are constipation or diarrhea with mushy or pebbly stools of small calibre, abdominal cramps aggravated during peristaltic stimulation, palpable and tender sigmoid colon, and certain minimal mucosal changes in the rectosigmoid as observed through the sigmoidoscope. In the present series abdominal pain was the only constant finding. The authors do not deny the real probability that mucous colitis may exist in the absence of a history of abdominal pain, and a few such cases may have been overlooked. Abdominal pain, whether sharp, cramp-like, or present as a sensation of pressure or "gas," is so common, however, that its presence was considered the one constant finding in the syndrome.

In view of previous clinical observations on the inconstancy of constipation and diarrhea, the variability in the type of stools, the manifold locations and types of abdominal pain, the frequent occurrence of upper gastrointestinal disturbances, the association of cardiovascular symptoms, the frequently reported significance of allergic factors, and the possible rôle of excess catharsis as an etiological factor, a master chart was prepared incorporating these and other data considered to be significant. Statistical conclusions drawn from that chart are reported herewith. Most of the data were completed for every patient and percentages in most instances are based on the study of that number. In a few instances some data are missing for a small number of cases, but all percentages are based on the study of at least fifty-four.

Table I

Initial Diagnoses on First Admission to Hospital. Note the multiplicity of conditions with which mucous colitis may be confused. The eight unlisted diagnoses were correct but unrelated.

Diagnosis	No.	Per Cent
Colitis	22	37.0
Psychoneurosis	17	28.0
Gall-bladder disease	3	5.0
Appendicitis	2	3.3
Peptic ulcer	2	3.3
Cancer of stomach	2	3.3
Irritable heart	2	3.3
Addison's disease	2	3.3
All others	8	13.3

Mucous colitis is a disease whose onset usually occurs in early adult life. The average age of onset of symptoms was 23.4 years. Two cases developed before the age of 10, seventeen cases between 10 and 20, twenty-six cases between 20 and 30, eleven cases between 30 and 40, while only four cases developed after the fortieth year. The average age at the time of this study was 35.8 years, indicating a fairly long average prediagnostic period. The initial diagnoses of the patients in this series are enumerated in table 1.

In 38 instances the original diagnosis was other than "colitis." In some instances the original diagnoses were correct additional diagnoses, e.g. psychoneurosis, irritable heart, pregnancy, myxedema, asthma, allergy, diaphragmatic hernia, and peptic ulcer and Addison's disease each in one instance. All the remainder were frank errors. These aberrant diagnoses were for the most part suggested by one or another of the protean mani-

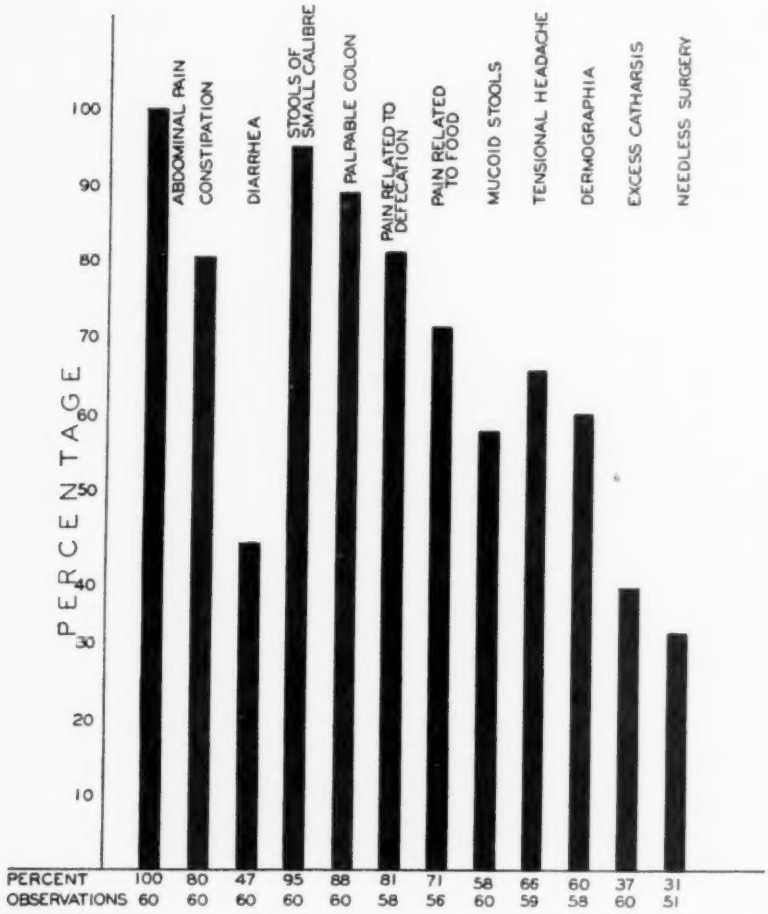

FIG. 1. Findings associated with mucous colitis. Abdominal pain is the most constant symptom, while constipation occurs almost twice as frequently as diarrhea.

festations of illness afforded by sufferers from mucous colitis, whether abdominal, cardiovascular, or neurasthenic in nature.

The frequency of the multiple symptoms and signs of mucous colitis is shown in figure 1. Eighty per cent of the patients had constipation at some time in the course of the illness whereas only 47 per cent had diarrhea. Indeed the majority of the patients with diarrhea gave a history of previous

constipation of the type characteristic of mucous colitis. In many instances patients with infrequent small mushy movements were unable to decide which appellation to employ. Patients with this type of constipation complain as a rule not of large, hard, painful dejections, but rather of an absence of any urge to defecate. Their movements, when they occur, are either composed of multiple hard, dark, spheroidal "rabbit pellets" or else are small, mushy, and described as "the size of a pencil." This type of constipation is aggravated by high cellulose diets, over-exercise, and cathartics, is relieved by low residue foods, relaxation, and atropine derivatives. There is evidence that it is due in part to spasm of the descending colon, sometimes with cecal retention and that it corresponds with Stierlin's [2] "constipation of the ascending type" and Fleiner's [3] "spastic constipation." The authors believe, on the basis of data presented elsewhere, that this type of constipation and mucous diarrhea are manifestations of the same bodily dysfunction, the former generally preceding and being milder than the latter. Mallory [4] suggested that spastic constipation, mucous colitis, and ulcerative colitis might represent progressive stages in the same process. Inasmuch as no patient in this series developed ulcerative colitis under observation, and inasmuch as many cases of ulcerative colitis begin suddenly without antecedent spastic constipation or mucous diarrhea, Mallory's supposition cannot be confirmed on the basis of this study. The types of stools encountered in patients with constipation and with diarrhea are shown in figure 2. It will be noted that even in the constipated group of patients small mushy movements are encountered with greater frequency than any other type.

Certain factors tending to precipitate pain are recorded in figure 1. To these factors must be added others which predispose to it in a more general way. Such factors are physical exhaustion, athletic "softness," fatigue, infection, emotional tension, and the like. The significance of such factors is discussed below. The locations at which pain was most frequently encountered are illustrated in figures 1 and 3. The most common single location was the left lower quadrant, where pain was found in 78 per cent of the cases. Lower abdominal pain occurred in 95 per cent, while discomfort was limited to the upper abdomen in only 5 per cent. Pain occurred more frequently at multiple sites than in one location alone. When limited to one location the left lower quadrant was most commonly involved, the upper abdomen and right lower quadrant being much less frequently the site of discomfort.

From figure 1 it is apparent that pain occurred following the ingestion of food in 71 per cent of the cases. In some cases this served as a differential diagnostic point from peptic ulcer, in which food relieves the abdominal pain. The aggravation of pain following the ingestion of food is presumably due to stimulation of the gastrocolic reflex. In about 80 per cent of the cases there is a definite association between the desire for defecation or the act of defecation and periods of aggravation of abdominal pain. This, again, is supposedly the result of colonic activity.

Lower abdominal pain was described as being "cramp-like" in 66 per cent of the cases. It was described as a sensation of pressure or of "gas" in 30 per cent, and was described as being sharp in 13 per cent. Some patients employed more than one term in describing it. "Cramps," "pressure," and "gas" were described with equal frequency in the upper abdomen, whereas sharp upper abdominal pain was described in only 10 per cent of the cases. Occasionally a patient complained of a burning sensation, commonly referred to in the literature as "pyrosis coli," and at times patients described granular sensations as if two pieces of sandpaper were rubbing together.

The physical findings in mucous colitis are few. The only statistically tabulated finding pertinent to the syndrome itself is palpability of the colon. The colon was found to be palpable in 91 per cent of the cases. In most cases the sigmoid was palpable as a firm contracted "rubber hose" while the cecum was often found to be distended and tender. The other physical findings frequently encountered were those of the anxiety state: widely dilated pupils, tachycardia, excessive sweating, cold, moist hands, hyperreflexia, taut muscles in the back of the neck, flushing of the neck and chest, tremor of the hands, etc. An excessive red response to stroking of the skin was encountered in 60 per cent of the cases.

There are no specific diagnostic laboratory procedures. The sigmoidoscope, however, does reveal changes which are definite and are suggestive of the condition. Such changes were found in 89 per cent of the patients in this series. According to Friedenwald, Feldman, and Rosenthal[5] the development of the sigmoidoscopic picture may be divided into three phases:

Stage 1. Vessels engorged with dilation of mucosal capillaries. Mucous membrane covered with glairy mucus. Slight granularity lending "shad roe" appearance.

Stage 2. Generalized injection against which vessels no longer stand out clearly. Surface drier with no glare. Disappearance of light reflex. Mucus dry and tenuous, appearing in patches on mucosal surface.

Stage 3. Mucous membrane thinned out, pale, covered with mucus. Pin point ulcerations on removal of surface mucus.

A moderate amount of spasm may be present in any of the three stages. These changes are not specific for mucous colitis. They may be present in the normal colon after irritant enemata, in the course of infectious enteritides, or in diseases in which there is irritation in proximal portions of the colon, e.g. proximal ulcerative colitis, diverticulitis, carcinoma, etc. There are also a few patients with the earlier manifestations of mucous colitis in whom no changes are observable. Our experience and that of two other groups of workers[5, 7] are in close agreement as to the value of the sigmoidoscopic examination (table 2). Although in this study no attempt was made carefully to delineate the three stages, the findings were closely in agreement with those of Friedenwald, Feldman, and Rosenthal.

In contrast with direct sigmoidoscopic observation, the routine barium enema is of comparatively little value from a diagnostic standpoint. In the present series spasm was seen in only 18 per cent of the cases which were so examined. Yet Friedenwald, Feldman, and Rosenthal found spasm to be the most common roentgen-ray finding. In their series it occurred in 51 per cent of the cases. Jordan and Kiefer [6] found spasm in 27 per cent and Bockus, Bank, and Wilkinson [7] in 43 per cent. Despite their lack of diagnostic value, the changes observed by roentgen-ray methods are of interest in explaining the disturbed physiology which characterizes this disease. The observation of the head of the barium column after oral ingestion is said by Kantor [8] to yield the most significant results. By this technic one may see that the barium column travels faster than is normally the case, the head of the column often reaching the splenic flexure in six hours instead of nine. The distal portion of the colon is often "pulled out" with flattening of the haustrations and spasm and may contain flakes or streaks of barium. At times these assume a stringy or ropy appearance, which Crane [9] has called the "string sign." It was originally described by Schwartz.[10] Information may also be obtained from carefully administered non-irritating enemata after preparation of the colon with saline irrigations. The barium must be introduced slowly and at a pressure not greater than 30 inches of water. Under these conditions, as Kantor points out, the colon is seen to fill more rapidly than normally, and the filling is accompanied by abnormally severe pain. The amount of fluid required to fill the colon is found to be only 32 ounces instead of the 36 to 40 ounces usually required. Spasm and flattening of the haustra of the descending colon are also frequently observed. Sometimes the pulled-out appearance of the descending colon is described as redundancy. Often there are abnormally deep haustrations in the transverse colon. Schwartz showed that in some cases the irritability was so great that mass spasm of the descending colon could be observed. Schatski [11] in studying one of the cases in the present series under controlled conditions was able to confirm the widely accepted observations described above. In addition pressure over the left side of the abdomen produced mass spasm of the descending colon and relaxation of the transverse colon while pressure over the midepigastrium produced spasm of the transverse colon and relaxation of the descending colon. All these changes are of physiological importance, but in view of the uncontrolled conditions under which routine roentgen-rays are made, the evaluation of such changes is extremely difficult. Furthermore, inasmuch as spasm is a transient state, it may at the time of any given examination fail to be seen (table 2).

Blood and urine studies in mucous colitis are normal. Eosinophilia, which might be expected because of the similarity of the disease to bronchial asthma, is usually absent. The stools are not remarkable except as to size, shape, color, consistency, and the presence or absence of mucus. The types of stools seen in patients with constipation and with diarrhea respectively are shown in figure 2 and are discussed elsewhere.

TABLE II

Incidence of Clinical Findings as Reported by Four Groups of Workers. There is general agreement as to the sexual incidence, the frequency of abdominal pain and of associated upper abdominal symptoms. There is close agreement as to the frequency of constipation and as to the value of sigmoidoscopic examination. There is more divergence of opinion as to the occurrence of diarrhea and regarding the value of examination by roentgen-ray.

	This Study	Friedenwald, Feldman, and Rosenthal	Bockus, Bank, and Wilkinson	Jordan and Kiefer
Upper abdominal pain or dyspeptic symptoms	48%	64%	58%	59%
Abdominal pain	100%	93%	70%	90%
Constipation	80%	72%	80%	80%
Diarrhea	47%	19%	44%	9%
Males	27%	16%	36%	23%
Females	73%	84%	64%	77%
Sigmoidoscopic changes	89%	89%	92%	—
Spasm by roentgen-ray	18%	51%	43%	27%
Food allergy	3.3%	1%	—	—
Coincident peptic ulcer	6.7%	8%	4%	—
Average age	36	30	36	30

There is some confusion in terminology with reference to the mucous colitis syndrome. Most clinicians fail to diagnose those forms in which diarrhea is not the predominating symptom. Hence the majority of medical men are taught to employ the term only in referring to the relatively small group in which intractable chronic mucous diarrhea is the primary finding. That this limited group fails to represent many cases with symptoms due to abnormal function of the colon is apparent. Jordan and Kiefer use the term "irritable colon" to include a very wide range of intestinal complaints, even to the point of making that diagnosis in 33 per cent of the patients seen in their gastrointestinal clinic. We have chosen a middle course and employ the term "mucous colitis" more broadly than is done by the average clinician. Yet we restrict it to those patients in whom there is good clinical evidence of colonic involvement. That there is not too wide a discrepancy in the minds of workers in the field is attested by table 2 in which the findings obtained in four moderately extensive surveys are shown in parallel columns. Note that Jordan and Kiefer found diarrhea in only 9 per cent of their cases indicating the wider range of patients included in their series. In all four series, however, the incidence of upper abdominal symptoms, abdominal pain, etc. are comparable. Sigmoidoscopic changes were noted in almost exactly the same percentage of cases in the series in which such observations were made.

II. MECHANISM

Hypotheses as to the etiology of mucous colitis are inextricably bound up with the history of the disease. DaCosta described in 1871 seven cases of severe mucous colic. He was conversant with the cases of diarrhea suffered by the soldiers during the American Civil War and recorded by Woodward.[12] DaCosta observed the similarity between them and the patients in his series.

He described the clinical syndrome with accuracy, noting the frequency of abdominal pain, of dyspepsia, and, surprisingly, of associated mucous discharge from the uterine cervix. He studied the rectal mucosa through a speculum and described its angry red and thickened, but non-ulcerated, ap-

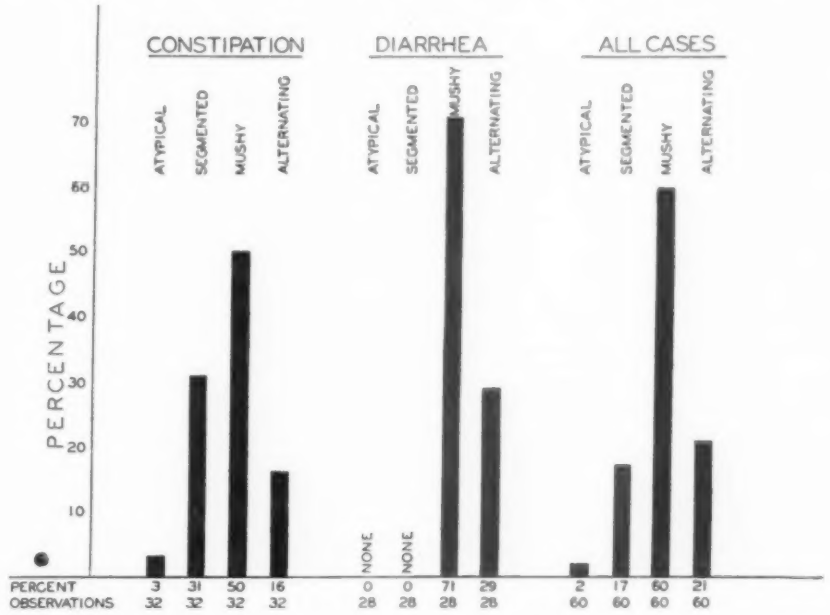

FIG. 2. Types of stools in mucous colitis. All stools are small in calibre except those listed as atypical. Mushy stools occur most frequently even in the patients suffering only from constipation. Small segmented pellets occur only in that group.

pearance. He recognized the tense, emotionally unstable nature of the patients, and he concluded that the disease was a manifestation of nervous tension and physical disability. In his original paper are numerous references to the classical authors who were aware of the rôle of emotion in the production of diarrhea. To DaCosta belongs the credit for elevating "Membranous Enteritis" to the dignity of a syndrome. After DaCosta's contribution great interest in the syndrome developed in Europe. The earlier European writers, Nothnagel,[13] Marchand,[14] and vonLeube[15] emphasized the concept that the disease was really a secretory and motor neurosis of the intestine, while their immediate followers, Einhorn,[16] Boas,[17] Ebstein,[18] and Schutz[19] disagreed to a certain extent with this simple concept. All the latter workers tended, rather, to emphasize the rôle of inflammatory processes in the colon, a view which among contemporary writers is exemplified by Niles.[20] VonNoorden[21] in reviewing the evidence for these two beliefs, emphasized the fact that paroxysmal attacks of pain with mucous diarrhea were at times observed in patients with infectious enteritides, but he was impressed by Rothmann's[22] and Hemmeter's[23] findings at the autopsy table of

histologically normal colons in persons who had suffered from severe " colica mucosa " attacks. Nothnagel realized that cramps and mucoid stools could occur in the presence or absence of focal lesions, and he divided his cases accordingly. Westphalen [24] attempted to reconcile these views by formulating the arm-chair concept that all excess mucous secretion was due to nervous impulses, which however, in the infectious enteritides were secondary to inflammation.

In the years following this controversy no one has succeeded in isolating an infectious organism, while further evidence as to the unstable nervous systems of the sufferers has been advanced. DeLangenhagen [25] in 1903 reported a series of 1200 cases, all of which he described as being neurotic. He emphasized manifestations of vascular instability, and he commented on the frequency with which symptoms of severe anxiety were encountered. Subsequent European contributions were largely radiological in nature, throwing light on the disturbed motility of the colon discussed elsewhere. At the end of the First World War Hurst,[26] as Woodward and DaCosta had done before, pointed out the frequency of diarrhea among the soldiers and the frequent coexistence of diarrhea and cardiovascular instability.

After that war interest in the mucous colitis syndrome again returned to this country. Allergy as an etiological factor in a small number of cases was established by Duke [27] and Hollander.[28] Attempts at establishing an allergic disturbance as the cause of a larger number were also made [29] and the rôle of bacterial allergy was investigated.[30]

Less immediately related to the clinical syndrome of mucous colitis the whole field of the autonomic nervous system was tilled, light was thrown upon the chemical mediation of nerve impulses, and on the central representations of the autonomic nervous system. Experimental surgery, clinical observation of neurosurgical patients, and pharmacological studies confirmed adequately this last relation. The work of Cannon and Britten,[31] Bard,[32] Cushing,[33] Light, Bishop, and Kendall,[34] and Keller, Hare and d'Amour [35] is of pioneer significance. In the light of this background further evidence is accumulating which supports the belief that mucous colitis is a secretory and motor neurosis of the intestine.

White and Jones [36] succeeded in producing mucosal changes in many respects similar to those seen in mucous colitis by the topical application of pilocarpine and of physostigmine within the rectosigmoid. Pilocarpine was found to have an almost immediate effect in producing glairy mucous secretion, diffuse injection, wrinkling of the mucosa, and constant spasm with a squirming movement of the intestinal wall. The changes were maximal five minutes after application. Physostigmine was found to produce its effect more slowly. After five minutes the mucosa was seen to be pale and swollen, presumably due to the presence of edema. At the end of 15 minutes' time, however, mucous secretion, wrinkling of the mucosa into coarse folds, and spasm were constantly observed. The difference in time interval is presumably due to the different modes of action of the two drugs, pilocarpine

being a direct stimulant to parasympathetic activity, physostigmine merely serving to inhibit the action of cholinesterase upon the normally produced acetylcholine at the nerve endings. White and Jones also observed diffuse

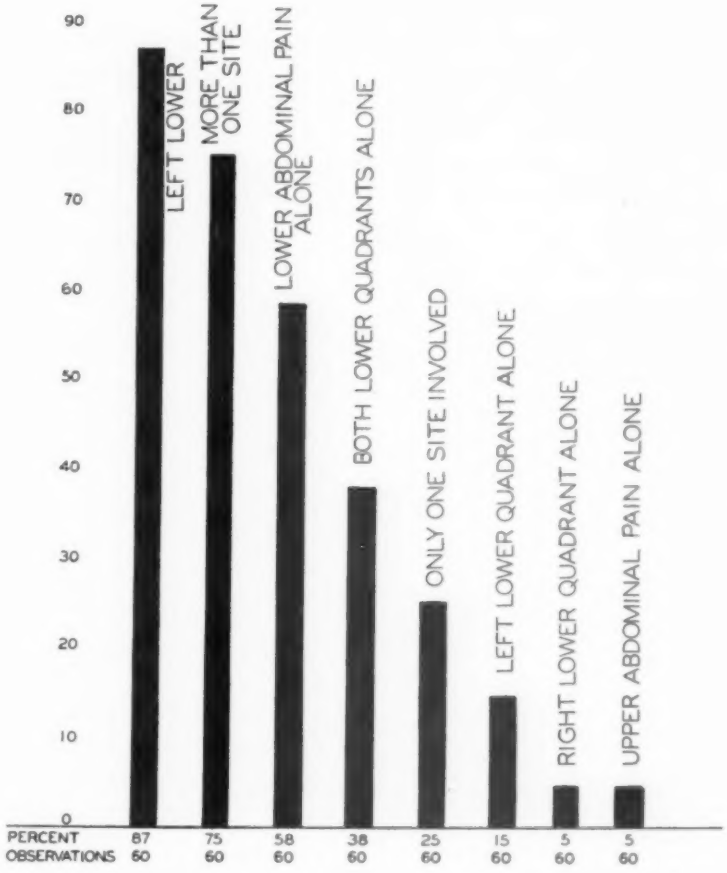

FIG. 3. Most frequent sites of abdominal pain. The left lower quadrant is almost invariably involved. Note that upper abdominal pain alone occurs in only 5 per cent of the cases.

changes in the rectal mucosa after the administration of large doses of acetyl-beta-methyl choline and of carbaminoylcholine by mouth. The mucosal changes produced in this way were almost identical with those described by Friedenwald, Feldman, and Rosenthal in the second stage of mucous colitis, i.e. diffuse injection with obliteration of venular markings, fine wrinkling of the mucosal surface, dull tenuous mucoid secretion, and inconstant spasm. Katsch [37] had previously demonstrated by observing roentgenologically the barium filled colon that pilocarpine and physostigmine produced increased depth of haustra in the transverse colon and areas of spasm and of increased motility in various portions of the colon. The small normal movements

often were suppressed and gave way to violent explosive movements. Katsch found the maximal change after pilocarpine to occur in 12 minutes after injection, while the maximal change after physostigmine did not occur for 30 minutes. Atropine was found to diminish tonus and movement, while adrenalin produced complete cessation of movement.

The evidence for the production of colonic changes similar to those seen in mucous colitis by stimulation of the parasympathetic nerve endings is essentially complete. What is lacking is evidence that innervation of the bowel via parasympathetic nerve fibers will produce these changes. Unfortunately the pelvic nerve is so filamentous that it does not lend itself to direct stimulation either in man or in laboratory animals. Studies by Banting and Hall [38] and by Manning, Hall and Banting [39] show that mucosal lesions of the stomach and upper intestinal tract result not only from prolonged intravenous administration of acetylcholine but also from prolonged direct vagus stimulation. These experiments suggest that stimulation of the sacral division of the parasympathetic nervous system, if practicable, should also produce mucosal changes in the bowel.

A number of conditioning factors seem to play a rôle in the production of symptoms in mucous colitis. Among these are direct irritants of the colon, such as rough foods, cathartics, enemata, and coincidental colonic infections such as acute enteritis, or amebic or bacillary dysentery. Factors which produce instability of the autonomic nervous system are also important. These include general infectious diseases, particularly influenza and "grippe," sudden weight loss, and physical "softness." White, Cobb, and Jones [40] showed that patients with mucous colitis had extremely low physical efficiency scores both in terms of the Schneider [41] and Turner [42] tests. These are tests of cardiovascular stability which correlate moderately well with athletic fitness. Specific food allergy is a factor which appears to be important in a small number of cases.

Many investigators [1, 13, 14, 15, 25, 7, 40] have shown emotional factors to be extremely important. There is evidence that in the given individual symptoms may occur only when a number of these factors are concurrently present.

III. Rôle of Emotional Tension

Sixty cases of mucous colitis were reviewed clinically. Of these, 57 were studied psychologically in sufficient detail to justify certain conclusions regarding the personalities of the sufferers and the rôle of emotional tension in precipitating the symptoms. These 57 cases were divided into two groups, a more neurotic group handicapped by psychoneurotic symptoms or by personality problems, and a less neurotic group composed of persons whose personality problems were not incapacitating. The severity of mucous colitis symptoms was not used as a criterion for this line of demarcation. An attempt was then made to determine in which patients exacerbations of symptoms occurred in association with readily understandable causes for

emotional tension. It was found that in four of the patients in the less neurotic group there was no relation between emotional tension and the development of symptoms. Two of these cases had their colonic symptoms in association with hives, and there is other evidence that they were allergic. A third patient had residual symptoms after emetine treatment for *E. hystolytica,* and the fourth presented symptoms and chemical changes strongly suggestive of Addison's disease. With these four exceptions all the 28 less neurotic patients showed a close relation between emotion and aggravation of symptoms. In the more neurotic group there were 29 patients. Of these only 17, or 58 per cent, showed a close relation between emotion and colonic symptoms. The discrepancy between the two groups is probably to be explained on the basis of the complicated chains of psychological processes in more neurotic persons, most of which are unconscious in nature. The subjective importance of any given stimulus may be greatly increased or decreased by these " long-circuiting " processes. The disapproval of a parent may be grossly accentuated, the loss of a fortune minimized. Hence it is difficult for the psychological observer to evaluate the tension producing quality of various experiences.

An attempt was made to classify the patients on the basis of conventional psychiatric diagnosis. On this basis no common denominator could be found. The less neurotic patients with psychogenic symptoms were all found to be suffering from a normal or exaggerated normal tensional response. They could be labeled as tensional states. Anxiety states and tensional states accounted for 14 per cent of the more neurotic patients, making a total of 63 per cent of the psychogenic cases. The remaining 37 per cent were fairly evenly divided among obsessive-compulsive states, depressive states allied to the manic-depressive group, hypochondriasis, and neurasthenia. There was only one primary psychiatric diagnosis of hysteria (1.7 per cent) and there were two more patients in whom hysterical tendencies or malingering were present (figure 4).

Although no one diagnostic label could be applied to all the cases, nevertheless there were certain personality characteristics and psychiatric symptoms which occurred with great regularity. From figure 5 it is apparent that tension was present in 96 per cent of the cases and anxiety in 82 per cent. Resentment was present in 92 per cent and guilt in 67 per cent. Depression, dependence upon others, asthenia, and rigidity of thought were also frequently encountered.

Flynn [43] called to the authors' attention his original observation that the inhibition of retaliation in a state of anger led to a confused response of the autonomic nervous system in which parasympathetic reaction was predominant. The mental state associated with inhibited anger is resentment. That resentment was so frequently encountered in this series is of interest in the light of Flynn's observations. Guilt, which was also frequently observed, is a sort of inward resentment directed against one's self. The quality of rigidity or inflexibility of thought, which was noted in 51 per

cent of the cases, is consistent with prolonged dwelling upon problems and hence abnormal continuation of resentment, guilt, anxiety, or other mental states.

An adequate review of psychiatric case histories is beyond the scope of this article. The following two summaries, however, show the type of

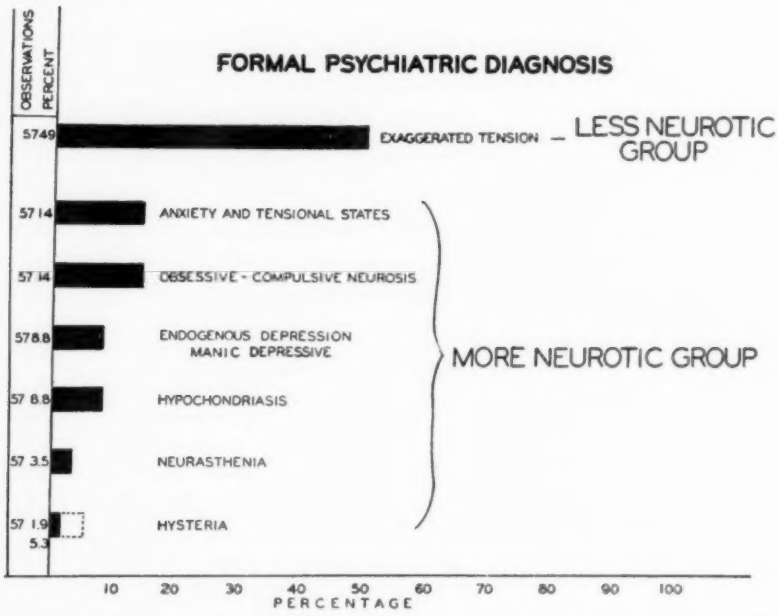

FIG. 4. Formal psychiatric diagnoses. There is no one diagnostic classification even for the patients in the more neurotic group. Note that hysteria (dissociative and dysmnesic state) is least frequently encountered.

reaction often encountered in less neurotic and more neurotic cases respectively. These two cases are chosen because their problems lend themselves to brief presentation.

Case 1. A 22-year-old, native born welder appeared in the medical clinic for the first time on October 16, 1936.

Chief Complaint: Constipation and epigastric pain of 10 months' duration.

Family History and Past Medical History: Essentially negative.

Present Illness: In January 1936 the patient first began suffering from constipation. He had one pebbly bowel movement every five days. He also developed epigastric pain, aggravated by meals, relieved by belching. This pain showed no relation to bowel movements, was not relieved by food. It became most severe in June 1936, and persisted in a discommoding degree until the time of admission to the clinic. On questioning, the patient said that he had definite cramp-like pains in both lower quadrants of the abdomen which were aggravated in association with defecation.

Physical Examination: The patient was a slightly built asthenic man with no gross physical abnormalities. His pulse was labile, and his colon was palpable and tender.

Special Observations: Gastrointestinal roentgen-ray examination revealed no abnormality of the esophagus, stomach, or duodenum. Sigmoidoscopic examination showed no abnormality within the rectosigmoid.

Psychiatric Observations: The patient had a congenial and friendly father, but his mother was a strict and domineering woman with fixed and rigid ideas. He lived in moderate suburban circumstances with his parents and a sister. He had had a high school education, one year of business training, and had been employed as a welder for three years. When he was eighteen years of age he had met a Protestant girl and introduced her to his mother, who heartily approved of her. He became engaged to the girl, saw her every few months, and wrote to her several times a week.

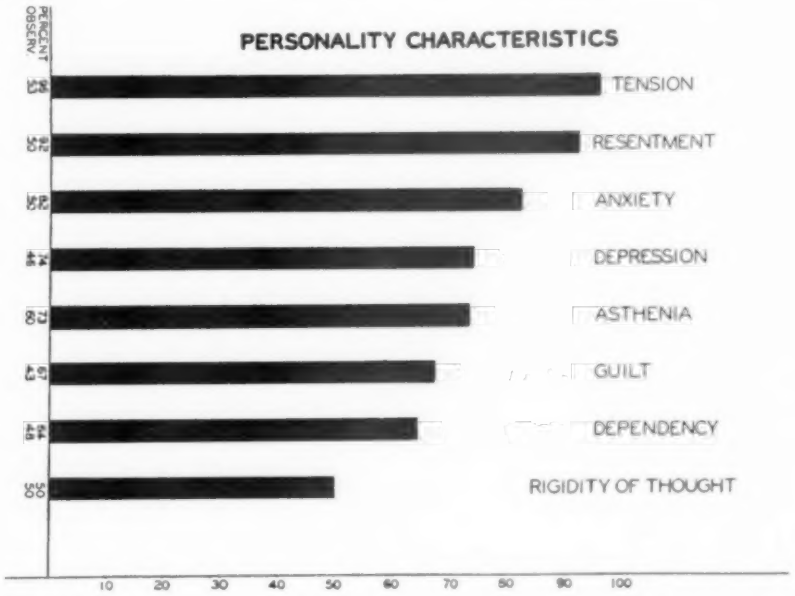

FIG. 5. Personality characteristics of patients with mucous colitis. Tension is the common denominator present in almost the entire group. The rôle of other factors in maintaining tension is discussed in the text.

In December 1935 he decided that he was no longer sexually attracted to the girl and that the time had come to break his engagement. He did so against the loudly voiced objections of his mother in January 1936, the very month of the onset of his symptoms. Immediately thereafter he began to devote his attentions to a young Catholic girl. This was entirely unacceptable to his mother, who was a Methodist. The tension grew more heated, and in June 1936, resulted in the patient's leaving home for the summer. This was the time at which symptoms were most severe.

Course: The patient's symptoms were instantly relieved by the use of atropine derivatives and a low residue diet. He was reassured to learn that his symptoms were not those of a peptic ulcer and was quick to realize the significance of the tension which had developed with his mother. He developed a policy of continuing his attention to the Catholic girl, which his mother soon found she was unable to thwart. On the contrary she developed an affection for the girl and accepted the situation gracefully. In May 1937, the pair were married, settled eight miles from home, and enjoyed emotional and physical happiness. Symptoms continued to remain in abatement.

The only aggravation in symptoms after the patient came under observation in October 1936, was when he became involved in a minor automobile accident which involved some litigation. During a period of a few days following the accident he had a recurrence of symptoms.

Case 2. A 35-year-old, native born spinster entered the hospital January 12, 1938.

Chief Complaint: Constipation of ten years' duration.

Family History: Essentially not remarkable.

Past Medical History: The patient had had in addition to the usual childhood diseases scarlet fever, diphtheria, influenza, herpes zoster, and pneumonia. She had had her appendix removed at the onset of the acute phase of her present illness. She had always suffered from easy fatigability, occasional palpitation, and headaches.

Present Illness: The patient was well until 10 years before admission to the hospital at which time she began to suffer from chronic constipation for which she began the occasional use of cathartics. Her illness was not severe, however, until 1935, at the age of 33, when it became grossly severe and was accompanied by cramp-like pain in the right lower quadrant of the abdomen. The pain was aggravated following the ingestion of meals, particularly those composed of rough foods, and was noticeably increased at times of emotional upsets. Her stools were hard, small, and composed of pellets. In addition to the increased severity of her constipation, at the time of admission she was developing upper abdominal symptoms, including epigastric distress, belching, sour eructations, heartburn, coated tongue, and bad breath, about which she was also concerned. In addition she developed almost constant nagging occipital headache, accompanied by tension of the posterior neck muscles and aching in the right trapezius region. All these symptoms remained unabated until her admission.

Physical Examination: The patient was a well developed and nourished, neatly dressed woman whose gestures were distinctly mechanical. Her descending colon was palpable and tender. She showed excessive sweating. Her tendon reflexes were hyperactive, but she had no tremor.

Special Data: A sigmoidoscopic examination revealed definite irritability of the rectosigmoid with some reduction in calibre. The mucosa was distinctly injected, and there was much glairy mucus present. The veins were prominently distended, standing out from the mucosal background.

Psychiatric Observations: The patient's father, the proprietor of a small butcher shop, had settled in a small city 10 years before the patient was born. Her mother was the disciplinarian of the family, and throughout the patient's life had been a thorn in her side. In school the patient had done well both academically and socially and had planned to go to the state normal school. This was impossible because of her father's circumstances, and because there was no local normal school in her native city. She felt bitterly about her inability to obtain this added education and bore overwhelming resentment against her parents: (*a*) because they could not understand her position in feeling that she needed this education, (*b*) because she felt that they might have been able to afford it had they made other sacrifices, and (*c*) because they had been so stupid as to settle in a manufacturing city when they might have settled in a city which boasted a normal school. Therefore, at the age of 19 she moved to another city and worked in an office. When she was 22, however, she returned home to nurse her ailing mother, and spent six miserable years at the task before her mother finally died. During this time she did take an evening course in beauty culture and after her mother's death spent some years working as a "beautician."

In 1935, at the age of 33, her most acute state of emotional turmoil developed. She went to a large city to take a short course in hairdressing. While there she consulted a young physician professionally. He was sympathetic and developed a real interest in her. She saw him on numerous occasions, felt that marriage to him was

likely, and yielded to his sexual advances with enjoyment. This engagement failed to materialize; the patient believed the failure due to the interference of the doctor's brother, who she felt disapproved of her and of her father's modest occupation. That this experience was one of extreme difficulty for her was attested by the inconsistency in her attitude toward this man, for whom she had only the most hateful of epithets, yet whom obviously she still loved. Discouraged and embittered she developed an acute exacerbation of her symptoms, had her appendix removed because of chronic abdominal pain, and began to develop her vague, generalized tenseness. It will be noted that her constipation originally developed during the early years which she spent in conflict over caring for her mother and that the acute exacerbation of these symptoms took place immediately after the collapse of her marital dream.

Course: Atropine derivatives immediately relieved the patient's upper abdominal symptoms and reduced to a great extent her constipation and lower abdominal cramps. However, in view of her age, her rigidity of thought, and her drift toward hypochondriacal complaints it seemed wise to recommend more intensive psychotherapy, and this was done.

In the first of these cases the cause of emotional tension is readily understandable on the basis of the life situation. It may be argued that many young men could solve similar problems without the development of undue tension, which is true. A modifying factor in this case is the importance attached by the boy to his mother's opinion. Such a sense of dependence upon the opinion of one's mother is normal in childhood but is normally lost in adolescence. In this instance the patient lost his maternal dependence at age 21 with no great difficulty and with complete resolution of his problem. He certainly is correctly classified in the less neurotic group, although if the same situation were to evoke the same response at age 30, such classification would be doubtful. In this case the close association between emotional tension and the development of symptoms is obvious.

In the second case the cause for tension is clear enough, provided one can accept the premises which seem reasonable to the patient. These premises, however, are based on a rigid adherence to an unreasonable attitude. To a more flexible and resourceful individual many avenues of escape would be possible. Yet because this patient could not view her problems from a broader aspect she remained shackled. This peculiar rigidity of thought, with resentment against others, guilt, depression, and tension were frequently encountered in persons with not dissimilar histories. In this instance the association between social events, emotional tension, and symptoms is obvious enough. In some of the other more neurotic patients, however, such a direct relation could not be observed. The psychological processes were apparently so complicated that the chains of thought leading to the development of tension could not be demonstrated by the conversational method.

The evidence for psychological tension as a precipitating factor in mucous colitis cannot be reviewed here. It suffices to say that histories similar to those recounted can be obtained from the great majority of patients with mucous colitis. Such evidence is adequately presented elsewhere.[7, 40]

Summary

The syndrome of mucous colitis is sufficiently clear for accurate diagnosis in the majority of cases. The diagnosis is applicable to a greater number of persons than are included in this group by the average clinician. "Mucous colitis" comprises a narrower group than is included by the term "irritable colon" as employed by Jordan and Kiefer. In general patients with mucous colitis suffer from constipation or diarrhea with some form of abdominal pain. In most cases the stools are small and are either mushy or composed of hard pellets. As a rule the symptoms are seen in persons who have labile autonomic nervous systems with concurrent cardiovascular instability, and are most pronounced in persons who are in poor athletic training. The lower abdominal pain is generally accompanied by upper abdominal symptoms such as nausea, heartburn, belching, and sour eructations. Cardiovascular symptoms such as palpitation, sweating, faintness, and neurocirculatory asthenia are often encountered. On physical examination the sigmoid colon is often palpable as a firm "rubber hose." The stigmata of instability of the autonomic nervous system, flushing, sweating, cold, moist hands, instability of the pulse rate, dilatation of the pupils, and abnormally red skin response to scratching, are frequently encountered. Instability of the cardiovascular system is further evidenced by so-called physical efficiency tests. The signs and symptoms, therefore, appear to be essentially those frequently noted in somatic neuroses such as neurasthenia and anxiety states.

Evidence is presented that changes in the rectosigmoidal mucosa similar to those seen in mucous colitis may be produced by the topical application of drugs which stimulate or simulate the action of the parasympathetic division of the autonomic nervous system. In some instances these changes may be produced by the oral administration of such drugs.

Certain observations on the frequency of psychogenic factors as precipitating agents in mucous colitis are also presented. In most instances mucous colitis appears to be a somatic response to a type of nervous tension. Mental states conducive to this response appear to be those of anxiety, resentment, and guilt. Associated depressive, neurasthenic, and hypochondriacal features are often present, but no one psychiatric diagnosis comprises the mucous colitis group. A rigid type of thinking, similar to that seen in obsessive-compulsive states, is present in 50 per cent of the cases and may play a rôle in prolonging periods of tension. The symptoms of mucous colitis appear to represent a clear-cut somatic response to tension and not to be psychologically determined and obviously gainful such as those seen in hysteria.

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TUBERCULOSIS AMONG STUDENTS AND GRADUATES IN NURSING*

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During the past decade there has been a widespread interest revived in the subject of tuberculosis among nurses, with particular emphasis on the transmission of the disease from patients to students and graduates of this profession. The danger of those who care for tuberculous patients contracting the disease has long been recognized, as evidenced by the following statement: "Isocrates (436–338 B.C.), pleading for the inheritance of a consumptive who had adopted him and whom he had nursed, exclaimed: 'I was in such a condition that all my friends, who came to visit me, expressed their fear that I perish with him, and pledged me to protect myself, telling me that most of those who had nursed this disease had become victims.'"

Aristotle said: "Why, when one comes near consumptives, or people with ophthalmia, or the itch, does one contract their disease, while one does not contract dropsy, apoplexy, fever, or many other ills? . . . In approaching the consumptive one breathes this pernicious air. One takes the disease because there is in this air something disease-producing."

In the literature of the centuries that followed there are numerous references to the contagiousness of consumption. A controversy was waged between those believing in the hereditary nature of tuberculosis and those believing in its contagiousness. Drastic laws were enacted and rigidly enforced to control contagion in such nations as Italy and Spain in the 18th century. It was not until the 19th century that overwhelming evidence was presented on the side of contagion through the experimental work of Klencke, Villemin, and Cohnheim, the epidemiological writings of Budd, and the bacteriological studies of Koch. During Koch's time tuberculosis was thought to be so prevalent that nearly every one had "a touch" of it. Pirquet found a high percentage of the young adults he examined to be tuberculin reactors. He was of the opinion that in the city in which he worked, as well as in the tuberculosis clinic, one might expect nearly all young adults to be infected, but he was inclined to believe that in other parts of the world, where there was not so much exposure of children to contagious cases of tuberculosis, the incidence of reactors would be lower.

Actual observations did not prove the point conclusively in this country until 1916 when Veeder and Johnston of St. Louis found that less than 50 per cent of school children reacted to tuberculin, and in 1924 when Slater

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found that only slightly more than 10 per cent of the school children of a rural community had been infected with tubercle bacilli. These observations may be looked upon as great landmarks of progress and of advancement of our knowledge of tuberculosis, for they were the beginning of a new era in the study of this disease. They so informed, inspired, and encouraged, that workers everywhere took heart. Ever since Slater reported his work the tuberculosis control program has rapidly increased in intensity and accomplishment. Large tuberculin testing programs were instituted, and it again became perfectly obvious that tuberculosis is contagious, when the workers administered tests and found that nearly all who were in direct contact with persons in the consumptive stage of tuberculosis became reactors. This stimulated efforts for the provision of places to isolate tuberculous patients in order to break or prevent contact between them and the uninfected. This was accomplished to such a degree that in many places the majority of girls and boys grew to adulthood without having been contaminated with tubercle bacilli. A problem as old as the disease itself now could be definitely proved to exist, namely, the spread of tuberculosis from the patients who had been isolated in institutions to protect their families and communities to those who cared for them in these institutions, particularly the nurses, both students and graduates. Wherever the tuberculin test was administered to students of nursing on entrance, during, and at the end of their course, a marked increase in the number of reactors was found to occur during training. In fact, in some places where only 30 to 50 per cent of the entering students reacted to tuberculin a full 100 per cent reacted before graduation, as reported by such authors as Heimbeck and Geer.

Boynton made observations on students in a school of nursing and students in a college of education. She found that "the tuberculosis infection rate is one hundred times greater in the student nurses on a general hospital service than in students in the college of education and five hundred times greater in student nurses on a special tuberculosis service than in college of education students."

Amberson and Riggins tested 539 student nurses and found that 57.9 per cent were reactors on admission. Of a group of 143 non-reactors on admission, who were followed six months to three years, 37 became reactors during the first year, 37 during the second year, and 10 during the third. Among 70 who were non-reactors on entrance, but were followed for three years, all but 10 became reactors.

Mariette says: "Still the possibility of infection exists in a sanatorium and this possibility constitutes a problem for the nurse who is caring for tuberculous individuals." In speaking of the nurse becoming infected he says: "In my opinion it is impossible for her to care for such patients very long without having an occasional bacillus gain entrance to her body."

Thus, although the tuberculosis situation with reference to infection had been markedly improved in the country as a whole, there had been created within the walls of our institutions a situation among our student nurses no

better than that of the time, place, and conditions of Pirquet's work. Along with this high infection attack rate among the students of nursing came the inevitable—mental anguish, illness, and death. With the recognition of the problem came attempts to solve it. Space does not permit more than a brief review of certain publications in this field, but the references contain many others.

The type of pulmonary lesions which students and recent graduates in nursing develop has been a subject of considerable controversy. In some series of cases reported there has been no previous tuberculin testing, and hence the determination of type is possible only through a long period of observation. In other series no attempt has been made to differentiate between the first infection and reinfection types, so that all lesions demonstrated by roentgen-ray film or otherwise are considered and treated as clinical disease. In other groups of cases a serious effort has been made to distinguish between the types of lesions which appear in the lungs, since treatment necessarily is dependent upon the type of lesion present.

Among 625 reactors on entrance to a school of nursing Heimbeck found that 27 developed conditions which he considered as evidence of clinical tuberculosis, whereas, among 280 who became reactors under his observation, 96 developed evidence of the disease in addition to the tuberculin reaction. However, in 39 of these students erythema nodosum and the tuberculin reaction were the only evidences of tuberculosis. Twenty-six others had only evidence of the primary complex located by roentgen-ray examination in the lung parenchyma, the hilum lymph nodes, or both. Sixteen others had pleurisy with effusion, two had fatal tuberculous meningitis, and 13 had clinical pulmonary tuberculosis.

Shipman and Davis of San Francisco, over a 10-year period of observation, found that between 6 and 7 per cent of the student nurses developed clinical tuberculosis and that an additional 4 per cent had developed the disease after graduation.

Among 110 student nurses observed by Geer of St. Paul, 5.5 per cent had developed lesions demonstrable by roentgen-ray or other phases of the examination by the time he made his report.

In 1934 Wicks of New Toronto, Ontario, wrote that "no nurse or attendant known to have entered his or her occupation with a positive tuberculin reaction has developed tuberculous disease during the past year, whereas six of those with a negative reaction on entrance have developed tuberculous lesions in the same period." Three of these persons had pleurisy with effusion; two had minimal parenchymal shadows with enlargement of the hilum shadows; and one mottling in the base of the right lung with evidence of small cavity formation and the presence of tubercle bacilli in the sputum.

Amberson and Riggins reported that among 492 student nurses eight developed new lesions while in school. Meulengracht found that 5 to 6.2 per cent of the nurses in a Danish training school developed tuberculosis.

In 1930 Ross reported 60 students and graduates in nursing admitted to the Manitoba Sanatorium during the previous five years. In a more recent report he states that 75 others have been admitted. He says: "There is no doubt that the tuberculosis morbidity among nurses, especially nurses in training, is excessive and apparently increasing, as our second series is larger than the first, in spite of the fact that a new sanatorium in the Province now shares these cases with us." Thus, he reports 135 students or graduates in nursing who have been treated in his institution. He says: "Scores of students of nursing lose health and life through hospital-contracted tuberculous infections. Practically all students become tuberculin-positive during their course, showing that they have become infected even if disease should not follow. The hospital cannot avoid responsibility for the infection of nurses until the utmost of medical and nursing science has been used to prevent it."

In Saskatchewan, Ferguson made some observations on tuberculosis among nurses from 1930 to 1933 and found that 12 times as many students or recent graduates fall ill from this disease as other persons in the general population, and eight times as many as among normal school students, mostly girls, of almost the same age as the nurses.

Soper and Amberson state that "the Yale School of Nursing has not suffered particularly from tuberculosis in recent years." Of 191 students, who had roentgen-ray films on entrance and again on graduation over the last five years, two developed minimal parenchymal lesions and one other had pleurisy with effusion.

Badger and Spink observed student nurses in the Boston City Hospital with reference to tuberculosis over a five year period beginning January 1932. Of the 470 nurses observed 57.11 per cent were reactors on entrance to the school. Of the 126 nurses who completed their course 90 per cent were reactors on graduation. During this period of observation eight students developed lesions which were located by examination. One of the eight reacted to tuberculin on admission to the school; the remaining seven were non-reactors on admission but became reactors while in school.

Malmros and Hedvall examined 3,336 students and nurses and found 133 (4 per cent) with active tuberculosis. From this beginning they continued their studies, during which they observed 151 cases of fresh primary infection in adults, 104 of whom were free from symptoms and exhibited no evidence of disease except the tuberculin reaction. In the remaining 47, however, they were able to demonstrate lesions. These authors stated "that no less than thirty-five of these cases were students of medicine and nursing who through their work were exposed to massive infections of tubercle bacilli." From the examination and observation of 10,000 persons of various ages and various population groups in southern Sweden they stated that "the majority of cases of active tuberculosis in our material was among medical and nursing students. In this category of young persons one has to deal with an important occupational hazard."

In addition to those quoted many others have reported on tuberculosis among students and graduates in nursing. From the available reports it is evident that there is a considerable difference in the degree of severity of the tuberculosis problem in various institutions.

In 1929 we began observations on students on entrance and throughout their courses of training. Our procedure began with the administration of the tuberculin test to all entering students. Those who did not react to the first dose (0.1 milligram) were given a second dose (1.0 milligram). Those who did not react to the second dose were retested in a similar manner at six-month intervals as long as they were non-reactors. All who reacted to the tuberculin test on admission or who subsequently became reactors were to have roentgen-ray films made of their chests at once and annually thereafter, except those in whom the findings warranted more frequent examinations. At the beginning of our studies the recommendation of roentgen-ray film examinations was frequently ignored since the relationship between a tuberculin reaction and clinical tuberculosis was not apparent. It was difficult to convince the schools that a girl in apparent excellent health with a tuberculin reaction might have clinical disease developing which would cast a definite shadow on the roentgen-ray film. Therefore, our early data are not as complete as we had desired. However, during the latter part of our period of observation all the schools were coöperative to the fullest extent.

In 1938 we sent a questionnaire containing the following questions to those who graduated as non-reactors:

1. Have you had the tuberculin test repeated since you left the school of nursing? If so, please give approximate dates and the results; that is, was the test negative or positive?
2. If your test has become positive, have you had any roentgen-ray films made of your chest? If so, on what approximate dates and were any abnormal shadows found in your lungs?
3. Have you had any illness since leaving school, such as pleurisy or disease of the lungs?

The following questions were sent to those who were reactors on graduation.

1. Have you had any roentgen-ray films made of your chest since leaving the school of nursing? If so, on what approximate dates and were any abnormal shadows found?
2. Have you had any illness since leaving school, such as pleurisy or disease of the lungs?

School of Nursing II

In School II classes were admitted every year except 1933; therefore, there were no graduates in 1936. There was no tuberculosis service in this

school except during the year 1937, when the seniors were encouraged but not compelled to take a six weeks' service in a sanatorium. The second student who elected this service returned with a strong tuberculin reaction. A few weeks later the roentgen-ray film revealed definite evidence of a lesion in the left upper lung field. The tuberculosis service was completely abandoned the following year. Therefore, for the most part, the girls in this school of nursing have had only the contact with tuberculous patients which might occur in any general hospital. The results of our observations on tuberculin reactions are shown in table 1, where it may be observed that among the entering classes the percentage of reactors ranged from 0 to 29.2, whereas on graduation this percentage ranged from 28.7 to 55.0.

TABLE I

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation in School II

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	14	3	21.4	4	28.7
1933	24	7	29.2	9	37.5
1934	24	3	12.5	12	50.0
1935	20	4	20.0	11	55.0
1936	0				
1937	13	0	0	7	53.9
1938	25	1	4.0	10	40.0

Note: Those who became reactors in training and discontinued their course are included as reactors on graduation.

In this school 120 student nurses were observed, 18 of whom reacted to the tuberculin test on entrance; 35 became reactors while in school, and 67 did not react to tuberculin on graduation. Of the 18 who entered as reactors one developed a demonstrable clinical lesion before graduation. One student on entrance in 1932 reacted strongly to tuberculin. Films of her chest at that time were clear. In 1933 there was evidence of disease in the apex of the right lung and at the level of the second interspace in the left lung where evidence of cavitation soon appeared. Tubercle bacilli were recovered from the sputum. Another student entered the school of nursing in the fall of 1935 as a tuberculin reactor. Roentgen-ray film in the fall of 1935 revealed evidence of calcification in the right hilum. In 1937 roentgen-ray film revealed evidence of disease in the right upper lobe.

Of the 35 who became reactors one had erythema nodosum with no other evidence of disease, and one developed a primary lesion demonstrable by roentgen-ray film in the left upper lobe.

Among the 120 graduates of this school 59 (49.2 per cent) replied to our questionnaire. Twenty-five (47.1 per cent) of them were previous tuberculin reactors, and 34 (50.7 per cent) were among the 67 who were non-reactors at the time of graduation. In this latter group 12 had the

tuberculin test administered since graduation, two of whom had become reactors (16.6 per cent). Therefore, we now know of 55 (45.8 per cent) of the graduates of this school who have reacted to the tuberculin test. Of the 25 previous tuberculin reactors who replied to our questionnaire 12 reported having had recent roentgen-ray examinations of the chest, and of the 34 non-reactors who replied five reported such examinations. One nurse who was a non-reactor on graduation in 1933 reported having developed a condition of the ankle, following an injury, which was diagnosed tuberculous in March, 1938, but the roentgen-ray films of her chest were clear. She was found to be a tuberculin reactor in February 1938, after the injury to her ankle.

In table 2 the results of tuberculin tests and the lesions located on roentgen-ray film or otherwise are summarized.

TABLE II

School of Nursing II

(No Tuberculosis Service)

18 with primary complexes on entrance
  a. Lesions while in school 2 (11.1 per cent)
  b. Lesions since graduation 0
35 developed primary complexes while in school
  a. Lesions detected while in school 1 (2.8 per cent)
  b. Lesions after graduation 0
2 developed primary complexes after graduation
  Lesions detected 1

SCHOOL OF NURSING III

In School III classes were admitted every year, but the data for the class graduating in 1934 are incomplete; therefore, this class is omitted from our report. There was no tuberculosis service in this school, but in 1937 an increased number of advanced cases of tuberculosis was admitted. Therefore, until 1937 the girls in this school of nursing had such contact with tuberculous patients as might be found in any general hospital that admits the occasional patient for diagnosis and treatment and the occasional unsuspected case that is admitted for some other condition.

On entrance the percentage of reactors among the classes ranged from 10.3 to 35.0, whereas on graduation it ranged from 31.3 to 64.5 (Table 3).

In this school 204 student nurses were observed, 50 of whom reacted to the tuberculin test on entrance, 43 of whom became reactors while in school, and 111 of whom still did not react to the test on graduation. Of the 50 who entered as reactors three had demonstrable reinfection type of lesions at the time; none developed demonstrable lesions while in school. Of the 43 who became reactors while in school one developed a primary lesion, demonstrable by roentgen-ray film, which later resolved. Another student who entered as a non-reactor in 1933 reacted strongly to the test in March 1934. At that time a film of her chest revealed no evidence of disease. However, in December 1935 she was ill and there was definite evidence of

TABLE III

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation, by Classes, School III

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	29	3	10.3	15	51.7
1933	40	14	35	21	52.5
1934	Insufficient Data				
1935	44	12	27.3	18	40.9
1936	32	6	18.8	10	31.3
1937	28	5	17.8	9	32.1
1938	31	10	32.3	20	64.5

Note: All those who entered as non-reactors and became reactors in training are included as reactors on graduation.

areas of disease disseminated throughout the left lung and the upper lobe of the right lung. Tubercle bacilli were present in the sputum.

Unfortunately, in the earlier part of our work the roentgen-ray examination was not routine in this school; therefore, we saw only those students who actually developed symptoms.

Among the 204 graduates, 82 (40.2 per cent) replied to our questionnaire. Among the 93 who graduated as reactors, 34 (36.6 per cent) replied, and of the 111 who were graduated as non-reactors, 48 (43.3 per cent) replied. Twenty-three of those who were graduated as non-reactors reported having had the tuberculin test administered since graduation, five (21.5 per cent) of whom had become reactors. Therefore, we now know of 98 (48.0 per cent) of the graduates of this school who react to the tuberculin test. Of the 34 previous reactors who replied 23 have had recent roentgen-ray examinations of the chest, as also have 15 of the 48 previous non-reactors. Three of the graduates are known to have developed pulmonary lesions since graduation as follows:

Case 1. This nurse completed her training in 1931 as a non-reactor, after which she was engaged in private duty nursing. In 1935 she accepted a position in a hospital where she was in contact with tuberculous patients. Later the same year she was found to have definite evidence of disease in both upper lung fields. The tuberculin test was administered, and she was found to be a reactor. No symptoms have appeared and the shadows have decreased. She was treated by strict bedrest for approximately one year, but is now working on a full time basis.

Case 2. This nurse entered the school of nursing in the fall of 1929 and was graduated in the spring of 1932. Throughout the nursing course she was a non-reactor to tuberculin. Following graduation she was employed in a general hospital where she had contact with tuberculous patients. In 1937 a roentgen-ray film revealed evidence of a small area of disease in the apex of the right lung. She was admitted to a sanatorium in September 1937, and discharged in June 1938. At no time were any significant symptoms present. She is now working on a full time basis.

Case 3. This student entered the school of nursing as a non-reactor in the fall of 1931. Periodic tuberculin tests revealed no reaction throughout her course of nursing. Following graduation, in the spring of 1934, she was exposed to tubercu-

losis from August 1937 to March 1938, and in December 1937 she was found to be a tuberculin reactor. In March 1938 roentgen-ray films revealed a definite shadow in the right second interspace. She had no symptoms at any time. The last film, made in November 1938, revealed a marked decrease in the shadow. She did not discontinue her work on account of this lesion.

In table 4 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized.

TABLE IV

School of Nursing III

(No Tuberculosis Service)

50 with primary complexes on entrance
  a. Lesions while in school 0
  b. Lesions since graduation 0
43 developed primary complexes while in school
  a. Lesions detected while in school 2 (4.7 per cent)
  b. Lesions since graduation 0
5 developed primary complexes after graduation
  Lesions detected 3

SCHOOL OF NURSING IV

In School IV all students were required to spend six weeks in residence in a sanatorium before graduation. In this school it was found that 41 nurses had completed the course without having the tuberculin test administered within nine months of graduation; therefore, they are not included in this report. Table 5 shows that the percentage of reactors among the classes

TABLE V

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation, School IV

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	94	24	25.5	69	73.4
1933	85	40	47.1	64	75.3
1934	98	33	33.7	65	66.3
1935	87	23	26.4	54	62.1
1936	62	11	17.7	38	61.3
1937	62	15	24.2	40	64.5
1938	62	19	30.6	39	62.9

on entrance ranged from 17.7 to 47.1, but that on graduation this percentage ranged from 61.3 to 75.3.

In this school 550 student nurses were observed, of whom 165 reacted to tuberculin on entrance; 204 became reactors while in school; and 181 did not react to tuberculin on graduation.

Of the 550 graduates, 287 (52.2 per cent) replied to our questionnaire. From the 369 who were graduated as reactors 174 (47.1 per cent) replied. Of the 181 who were graduated as non-reactors 113 (62.4 per cent) re-

plied. Of the 79 non-reactors on graduation who replied and have since been tested 27 (34.2 per cent) had become reactors since leaving school. Therefore, we now know of 396 who have reacted to the tuberculin test. Of the 174 reactors on graduation 136 replied that they had recent roentgen-ray films of the chest, and of the 113 non-reactors on graduation 40 had such examination.

Of the 165 who reacted on entrance four developed demonstrable lesions while in school and two after graduation:

Case 1. On entrance to the school of nursing in 1930 this student reacted to tuberculin. Films of her chest in 1931 revealed no evidence of disease. In 1932, however, there was evidence of disease in the left first interspace. This shadow persisted, and in 1934 it had extended. At this time there was also evidence of disease in the apex of the right lung.

Case 2. This student reacted to the tuberculin test on entrance to the school of nursing in 1932. Films of her chest through 1934 were negative. In 1935 there was definite evidence of disease in the upper lobe of the left lung. This shadow persisted through 1936, but could not be visualized in February 1938.

Case 3. This student reacted to tuberculin when she entered the school of nursing as a sophomore in 1932. Films of her chest in 1932 and 1933 were negative. In 1934 there was definite evidence of disease at the level of the first interspace on the left side. Her disease later increased and she had a pulmonary hemorrhage. The left phrenic nerve was interrupted and later artificial pneumothorax was instituted.

Case 4. This student entered the school of nursing in the fall of 1930 as a tuberculin reactor. Roentgen-ray films of the chest in 1931 and 1932 revealed evidence of fibrotic and nodular disease in the left lung, extending from the apex to the second rib. This was also present in September 1933.

Case 5. This student entered the school of nursing as a tuberculin reactor in the fall of 1930, but the roentgen-ray films of her chest revealed no evidence of disease. She discontinued school for reasons other than health. However, in the fall of 1935 she was found to have extensive disease involving the left lung from the apex to the level of the fifth rib anteriorly. There was definite evidence of cavitation, and tubercle bacilli were present in the sputum. Adhesions prevented successful artificial pneumothorax. Thoracoplasty was performed in 1936. She is now working on a full time basis.

Case 6. As a freshman in the school of nursing, in the fall of 1930, this student reacted to the tuberculin test. The roentgen-ray films of her chest revealed no evidence of disease through August 1933. In November 1933 a small lesion was discovered in the left infraclavicular region. In March 1936 there was evidence of disease in the right upper lung field. She was later hospitalized, and in March 1938 had far advanced disease with cavitation involving the right lung. Thoracoplasty is now being performed.

Of the 204 who became reactors as students 19 developed lesions demonstrable by roentgen-ray film or otherwise while in school, and five after graduation. The following developed only primary lesions which were demonstrated by roentgen-ray film:

Case 7. In the fall of 1929, as a freshman in a school of nursing, this student was a non-reactor to tuberculin. In the fall of 1931 she was a reactor. In December 1931 there was evidence of disease in both upper lung fields. The shadows gradually decreased until September 1936, when they had almost completely disappeared.

Case 8. In the fall of 1932, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1934, when she was a definite reactor. All roentgen-ray films were clear until September 1935, when there was definite evidence of disease in the left second and third interspaces. The shadow had decreased somewhat in February 1936.

Case 9. In the fall of 1931, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1934. All roentgen-ray films were clear until May 1935, when an area of disease appeared in the upper lobe of the left lung. The shadow gradually decreased until the summer of 1937 when it had completely disappeared.

Case 10. As a freshman in the school of nursing, in the fall of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until April 22, 1934. On May 8, 1934, there was evidence of a small area of disease at the level of the right second interspace. The shadow increased somewhat during the next two or three months, when she was advised to take treatment. She never returned to school. Subsequent films, including those in the spring of 1936 and the summer of 1937, revealed no change in the shadow.

Case 11. In the fall of 1929, as a freshman in a school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until January 1934. At this time there was definite evidence of disease at the level of the first interspace on the left side. The subsequent films showed a gradual decrease in the lesion until 1936. Since that time, including the summer of 1938, the shadow has remained unchanged.

Case 12. In the spring of 1934, as a student of nursing, this girl was a non-reactor to tuberculin. Periodic tests revealed no reaction until the winter of 1937. At that time there was definite evidence of disease in the right second and third interspaces.

Case 13. As a freshman in the school of nursing, in the fall of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1937. On December 28, 1936, there was evidence of disease in the right second interspace. The shadow appeared essentially unchanged through April 1937.

Case 14. As a freshman in the school of nursing, in the fall of 1932, this student was a non-reactor to tuberculin. In the winter of 1934 she was assigned to a tuberculous patient who died of the disease. She had some minor illnesses in the spring of 1934 and cancelled out of school. In March 1934 she reacted to tuberculin. In the summer of 1934 she was found to have an area of disease in the right subclavicular region and was advised by her physician to take a six months' period of bed rest. She never returned to school, but in the summer of 1936 her physician stated that she was cured. In February 1937 the roentgen-ray film revealed small densities suggestive of calcium deposits at the site of the disease. In December 1938 she was apparently well.

Case 15. In the fall of 1933, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. On May 21, 1934, she was still a non-reactor. On April 22, 1935, she reacted to tuberculin. A roentgen-ray film of the chest in October 1933 was clear. In May 1935 a roentgen-ray film revealed definite evidence of disease in the right first interspace. Periodic roentgen-ray films through 1935 revealed no change in the shadow. In April 1936 the shadow had decreased in size. Throughout the remainder of 1936 there was no change. By September 1937 the shadow had completely disappeared. In February 1938 the film was apparently clear.

Case 16. In the fall of 1933 this student entered the school of nursing as a non-reactor. At that time films of the chest revealed no evidence of disease. In February 1934 a shadow appeared in the first and second interspaces on the left side, but the

tuberculin test was not repeated at this time. In March the shadow had decreased somewhat in size, and she reacted to tuberculin. This student cancelled her registration and we have been unable to obtain further information concerning her.

None of these students was ill and we consider them as not differing from all the others who became reactors, except that one of the primary foci in each case was so situated that it could be seen in a roentgen-ray film.

The following had pleurisy with effusion while in school:

Case 17. As a freshman in the school of nursing, in July 1929, this student was a non-reactor to tuberculin. In May of 1931 she was found to be a reactor. In the spring of 1931 she had pleurisy with effusion on the left side while taking a tuberculosis service. She was admitted to a sanatorium on June 1, 1931, where she remained until August 31, 1931. A roentgen-ray film in November 1932 revealed evidence of adhesions in the left costophrenic angle, but no evidence of disease in either lung. In February 1933 a film revealed no change. On December 23, 1938, she wrote that she was enjoying excellent health and was employed as an instructor in a school of nursing.

Case 18. As a freshman in the school of nursing, in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1935, when she was a reactor. All roentgen-ray films were clear until August 1935, when she had pleurisy with effusion on the right side. She cancelled out of school on March 8, 1936, but returned in the spring of 1937. In May 1937 the roentgen-ray film revealed evidence of disease in the left lung extending from the apex to the second rib, and in the second interspace on the right side. She again left school and was admitted to a sanatorium on June 28, 1937, where she remained until November 24, 1937, with a diagnosis of minimal pulmonary tuberculosis. At no time were tubercle bacilli found in her sputum. She has not returned to school.

Case 19. As a freshman in the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until October 1930, when she was found to be a reactor. A roentgen-ray film of the chest at that time was clear. In November 1930 she had pleurisy with effusion. After several months the fluid absorbed and roentgen-ray films of the chest were clear through the summer of 1938.

Case 20. As a freshman in the school of nursing, in the fall of 1930, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until May 15, 1933, when she was found to be a reactor. Previous roentgen-ray films of the chest were clear, but on May 19, 1933, pleurisy with effusion was present. The fluid had absorbed by the fall of 1933. In July 1933 a small area of disease was detected in the right lung at the level of the second and third interspaces. In November 1933 an area of disease was demonstrated in the first interspace on the left side. In January 1935 the shadow in the right lung was sharply outlined and that in the left lung had almost entirely disappeared. She was in a sanatorium from July 1936 to June 1937, when her disease was classified as arrested.

We look upon pleurisy with effusion in this group as a result of the sensitiveness of the tissues to tuberculo-protein and to endogenous reinfection from the primary foci.

The following developed demonstrable lesions which probably represent the reinfection type:

Case 21. On entrance to the school of nursing, in the fall of 1930, this student was a non-reactor to tuberculin. In the spring of 1932 she reacted to tuberculin, but

the roentgen-ray films of her chest revealed no evidence of disease. In December 1932 a small area of disease was found in the left lung at the level of the second interspace. In May 1933 the area of disease was considerably larger and there was possible beginning cavity formation. She was then admitted to a sanatorium and artificial pneumothorax was instituted. She was discharged from the sanatorium in August 1935, but continued on artificial pneumothorax treatment.

Case 22. This student was a non-reactor to tuberculin on entrance to a school of nursing in the fall of 1929. Roentgen-ray films of the chest at that time were clear. In July and August 1931 there was evidence of thickened pleura on the left side and a small area of disease at the level of the second interspace in the left lung. A tuberculin test was said to have been administered at this time but there was no reaction. In January 1934, although strict bedrest had previously been employed, a small area of disease was found at the level of the third interspace on the right side. At this time she reacted strongly to tuberculin. She has had prolonged strict bedrest, and although her general health is good she still has definite shadows in both lungs.

Case 23. This student was a non-reactor to tuberculin when she entered the school of nursing in the fall of 1929. Roentgen-ray films of her chest were clear. She was still a non-reactor in September 1930. On June 9, 1932, she was admitted to a sanatorium with diagnosis of tuberculosis of the spine. She was discharged May 20, 1934. Spinal condition was good in June 1937. Roentgen-ray films of her chest revealed no evidence of clinical disease at any time including February 19, 1938. She did not return to complete the course in nursing.

Case 24. This student did not react to tuberculin on entrance to a school of nursing in the fall of 1931. In the spring of 1933 she was a definite reactor. All films of the chest, including those of the spring of 1935, were clear. In the summer of 1935 there was definite evidence of disease in the apex and first interspace on the left side. She was hospitalized for four and one-half months but no symptoms appeared. The films revealed no change in shadow through February 1936. In August 1937 she had extension of lesion with cavity formation. She has since been treated by artificial pneumothorax.

Case 25. On entrance to a school of nursing, in the fall of 1932, this student did not react to tuberculin. Roentgen-ray films of the chest were clear. In the spring of 1933 she was found to be a reactor. Roentgen-ray films of the chest through July 1934 revealed no evidence of disease. In November 1934 there was a definite area of disease present in the left lung at the level of the first interspace. In April 1935 the area in the left lung had increased in size, and there was a definite area of disease in the right lung at the level of the third and fourth interspaces. In April 1935 there was evidence of definite increase of the shadow in the right lung. She was hospitalized and artificial pneumothorax was instituted in August 1935. Empyema was present in December 1935. In August 1937 the empyema had disappeared and she was still being treated by artificial pneumothorax in a sanatorium.

The following students who became infected while in school developed lesions which were demonstrated after graduation:

Case 26. When this student entered the school of nursing in the fall of 1930 she did not react to tuberculin. She remained a non-reactor through August 1933. In the spring of 1934 she was found to be a reactor. Although previous roentgen-ray films of her chest had been negative she now showed evidence of pleurisy at the left base. This evidence had disappeared by January 1935. In October 1936 she was found to have extensive pulmonary tuberculosis involving the lower half of the right lung. Tubercle bacilli were present in her sputum. Artificial pneumothorax was instituted in October 1936, and her lung is still collapsed.

Case 27. This student was a non-reactor to tuberculin when she entered the

school of nursing as a junior in the fall of 1931. She was found to be a definite reactor in April 1933. Roentgen-ray films of her chest in January and April 1933 revealed no evidence of disease. In August 1935 roentgen-ray film examination revealed evidence of disease involving the left lung at the level of the first and second interspaces. The shadows have remained unchanged.

Case 28. This student entered the school of nursing in the fall of 1934 as a non-reactor to tuberculin. She was still a non-reactor in 1935. In May 1937 she was found to be a reactor. Roentgen-ray films in June 1936 and September 1936 were negative. In May 1937 there was possible calcification in the left hilum. There was evidence of disease in the left lung at the level of the second interspace. This shadow was still present in May 1938, but could not be visualized in November 1938.

Case 29. This student entered a school of nursing as a junior in the fall of 1930, at which time she was a non-reactor to tuberculin. In the fall of 1931 she still did not react to the tuberculin test. However, in June 1932 she became a reactor. Roentgen-ray films of her chest on several occasions in 1932 and 1933 revealed no evidence of disease. In January 1934 she had pleurisy with effusion. The effusion absorbed, and in 1938 the lungs were clear on roentgen-ray film examination.

Case 30. On entrance to the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. When she was graduated in 1932 she was a reactor. In the summer of 1933 she was employed in a sanatorium. At that time the roentgen-ray film examination of her chest revealed no evidence of disease. Periodic films were clear through January 1936. On June 11, 1936, a shadow was present in the right lung at the level of the first, second and third interspaces. In August 1936 the lesion had increased in size. She was then hospitalized, and in February 1937 artificial pneumothorax was instituted. Tubercle bacilli were never recovered from the sputum, and there were no symptoms except a slight cough at the time she was admitted to the sanatorium. She was discharged from the sanatorium on June 15, 1937, but continued on artificial pneumothorax through December 1938.

The following seven former students graduated as non-reactors but later developed lesions:

Case 31. This student entered the school of nursing in 1929 as a non-reactor to tuberculin and did not react while in school or on graduation in 1932. Following graduation she was employed in a sanatorium, and in January 1933 was found to be a reactor. In 1933 she was found to have a shadow on the roentgen-ray film at the level of the right second interspace. In June 1933 the shadow had decreased in size. Subsequent periodic films revealed a gradual disappearance of the shadow. On December 1, 1938, there was evidence of a probable small calcium deposit at the site of the previous shadow.

Case 32. As a freshman in the school of nursing, in the spring of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction throughout her course. Films of her chest were clear in October 1934. Immediately following graduation in the spring of 1935 she was employed in a sanatorium, and in October 1935 she reacted to tuberculin. At that time films of her chest were clear. In December 1935 she had pleurisy with effusion. She was admitted to the sanatorium where she worked on December 28, 1935. Films of the chest in January 1936, after the fluid had absorbed, revealed no evidence of disease in either lung. However, in March 1936 there was evidence of a large parenchymal lesion with cavitation in the right lung. Artificial pneumothorax was instituted and she is still on that treatment in the sanatorium.

Case 33. This student did not react to tuberculin when she entered the school of nursing as a junior in October 1931. She was graduated in June 1933. In August and September of 1933 she worked in a sanatorium, and in the fall of that year was

found to be a reactor, but the roentgen-ray films of her chest were clear. In January 1936 there was definite evidence of disease in each lung at the level of the first interspace. No symptoms developed. Strict bedrest was instituted. She is still in a sanatorium.

Case 34. This student entered the school of nursing in September of 1931 as a non-reactor. She still did not react to the tuberculin test when she was graduated in 1934. She was later employed in a hospital which had a tuberculosis service. In April 1937 she was found to have evidence of scattered areas of disease in the upper one-third of the left lung. She was hospitalized from May 7, 1937 until June 24, 1937. On May 13, 1937, the left phrenic nerve was interrupted. No symptoms were present at any time. On discharge from the hospital she returned to her home to continue treatment.

Case 35. On entrance to the school of nursing in 1932 this student was a non-reactor to tuberculin. Periodic tuberculin tests throughout her course revealed no reaction. Immediately following graduation she was employed in a sanatorium for four months, after which she worked on a chest surgery service for some time. While working in the sanatorium, in 1935, she was found to react to tuberculin, but the roentgen-ray film of her chest was clear. In March 1937 the roentgen-ray film revealed definite evidence of disease in both lungs, with cavitation in the right. Tubercle bacilli were found in the sputum in April 1938. Films in August 1937 and April 1938 showed no change. In October 1938 there was evidence of definite decrease in the shadows, and the cavity appeared to be reduced in size. She has been treated only by strict bedrest.

Case 36. This student entered the school of nursing as a non-reactor in the fall of 1933, and was graduated in 1936 as a non-reactor. Following graduation she worked on a tuberculosis service, and in the fall of 1936 was found to react to tuberculin. Roentgen-ray films of the chest while a student, including March 1937, revealed no evidence of disease. In March 1938 she had pleurisy with effusion on the left side. There was still some fluid present in October 1938. Tubercle bacilli were recovered from the fluid.

Case 37. In the fall of 1933 this student entered the junior class of the school of nursing as a non-reactor, and she did not react to tuberculin on graduation in 1935. Following graduation she worked for approximately two years in a sanatorium. In January 1936 she was found to be a reactor. When she discontinued sanatorium work roentgen-ray films of her chest were reported as revealing no evidence of disease. In November 1938 she was found to have pulmonary tuberculosis, with cavity formation in the right upper lobe. She was then admitted to the sanatorium where she had previously worked and artificial pneumothorax was instituted.

In table 6 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized. See table 9 for types of lesions.

TABLE VI

School of Nursing IV
(Six Weeks' Tuberculosis Service)

165 with primary complexes on entrance
  a. Lesions while in school 4
  b. Lesions since graduation 2 } (3.6 per cent)
204 developed primary complexes while in school
  a. Lesions detected while in school 19
  b. Lesions since graduation 5 } (11.8 per cent)
27 developed primary complexes after graduation
  Lesions detected 7

School of Nursing I

In School I all students were compelled to spend three months during the senior year on a 30-bed tuberculosis service in the hospital. This service was abandoned in 1935, so the class graduating in 1938 was the first one to pass through the school of nursing after the tuberculosis service was removed from the hospital. The results of our observations on tuberculin reactions are shown in table 7, where it will be observed that among the entering classes the percentage of reactors ranged from 2.4 to 44.4, whereas on graduation this percentage ranged from 40.5 to 100.

Table VII

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation, School I

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	36	16	44.4	36	100
1933	41	5	12.2	37	90.2
1934	26	10	38.5	25	96.1
1935	30	6	20.0	28	93.3
1936	25	4	16.0	20	80.0
1937	26	6	23.1	22	84.6
1938	42	1	2.4	17	40.5

Note: Those who became reactors in training and discontinued their course are included as reactors on graduation.

In this school 226 nurses were observed, 48 of whom reacted to the tuberculin test on entrance, 137 of whom became reactors while in school, and 41 of whom did not react to tuberculin on graduation.

Of the 226 students in this school 140 (61.9 per cent) replied to the questionnaire. Of the 185 reactors on graduation 121 (65.4 per cent) replied, and of the 41 non-reactors 19 (46.3 per cent) replied. Nine of the previous non-reactors reported having had the tuberculin test administered since graduation, but none had reacted to the test. There were 58 (47.9 per cent) of the 121 former reactors who reported having had recent roentgen-ray film examinations of the chest, and four of the 19 previous non-reactors who reported having had such examination.

Of the 48 entering as reactors two had primary lesions demonstrable by roentgen-ray film on entrance which later resolved. The following later developed clinical disease:

Case 1. In the spring of 1929, as a freshman in the school of nursing, this student was a tuberculin reactor. Roentgen-ray films of her chest in 1929 and 1930 were clear. On April 30, 1931, cloudiness was reported over both apices. In November 1934 she had pleurisy with effusion.

Case 2. On entrance to the school of nursing in the fall of 1932 this student was a tuberculin reactor. Periodic roentgen-ray films made throughout her course of training revealed no evidence of disease. In the spring of 1937, while employed

as a nurse in a general hospital, she was found to have tuberculosis involving the left lung from the apex to the third rib and the extreme apex of the right lung. No symptoms were present. Artificial pneumothorax was instituted in the spring of 1937. She is still receiving this treatment and has continued to work.

Of the 137 who became reactors as students we know of the following 11 who developed demonstrable lesions while in school, and of three who developed lesions after graduation:

Case 3. As a freshman in the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. She was still a non-reactor in March 1930, but in September 1930 she was a reactor. No roentgen-ray film was made until July 1931, when there was evidence of disease in the left upper lung field, extending from the apex to the level of the second rib. In September 1931 the shadow had decreased somewhat, but she discontinued training in September 1931 because of the shadow. There were never any clinical manifestations.

Case 4. This student entered the school of nursing in the fall of 1929 as a non-reactor. She reacted to tuberculin in the fall of 1930. Roentgen-ray films revealed no evidence of disease. In July 1931 there was evidence of disease involving both lungs at the level of the first and second interspaces. Following this she was on bed-rest for a year, during which time the shadows on the roentgen-ray film decreased in size. She returned to school in 1932. In the spring of 1933 there was definite evidence of disease in the left lung, with evidence of small cavity formation. She was placed on treatment, but in November 1935 she developed tuberculous pneumonia in the base of the left lung and died in November 1936.

Case 5. When this student entered the school of nursing in the spring of 1930 she was a non-reactor to tuberculin. In May 1931 she reacted to tuberculin. Films of her chest were clear in March 1930, but in October 1931 there was evidence of disease in the right first interspace. She was hospitalized from October 8, 1931 until July 5, 1932. She discontinued training and did not return. Pneumothorax was instituted while in the hospital. She discontinued artificial pneumothorax in 1936 and apparently was in good health in December 1938.

Case 6. As a freshman in the school of nursing, in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until February 1933, when she was found to be a reactor. Roentgen-ray films of the chest were clear until February 1933, when there was evidence of disease in the left upper lobe. In March there was evidence of effusion in the left pleural cavity. In April the fluid had practically disappeared, but the left costophrenic angle was obliterated. In June 1935 there was evidence of Ghon tubercle formation in the left lung at the site of the previous area of disease. At this time there was also seen a small but definite area of disease in the extreme apex of the left lung. She was apparently in good health in December 1938.

Case 7. This student entered the school of nursing as a non-reactor in the fall of 1932. In the spring of 1933 she reacted strongly to tuberculin. In the summer of the same year an area of disease was located in the right lung at the level of the first and second interspaces. By February 1934 this shadow had completely disappeared. In March 1934 she was found to have tuberculous pneumonia involving the right upper lobe. She later developed empyema, and died in May 1935.

Case 8. As a freshman in the school of nursing, in the fall of 1932, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until March 1934, when she was found to be a reactor. Roentgen-ray films of the chest were clear until August 1934, when there was evidence of fluid on the left side. She cancelled her registration and did not return until January 1936. At this time the only abnormal finding was partial obliteration of the left costophrenic angle. No

change was observed in July 1937. She was graduated in 1937, and in December 1938 she was working as an operating room nurse, apparently in excellent health.

Case 9. In the fall of 1932 this student entered the school of nursing as a non-reactor. She did not react to tuberculin until March 1934. In April of the same year a small area of disease appeared in the base of the right lung. In May 1934 this had definitely increased in size. Because of the occurrence of a small pulmonary hemorrhage, and the finding of tubercle bacilli in the sputum, artificial pneumothorax was instituted. She was graduated in 1936 and has continued on artificial pneumothorax treatment.

Case 10. As a freshman in the school of nursing, in the spring of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until October 1935, when she was found to be a reactor. All films of her chest were clear through September 1935. In April 1936 a lesion was present in the left lung extending from the apex to the first interspace. No treatment was administered, and in December 1938 she was working full time as a school nurse.

Case 11. This student entered the school of nursing in the fall of 1934 as a non-reactor to tuberculin. There was no test in 1936. She was a reactor in March 1937. Pleural effusion was found May 1, 1936, on the right side, and was still present June 5, 1936. In June 1937, the effusion was gone and her chest was clear.

Case 12. As a freshman in the school of nursing, in the fall of 1934, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1936, when she was found to be a reactor. In 1934 the roentgen-ray film of her chest was clear. In October 1936 there was evidence of disease at the level of the second rib on the right side. Films made on December 13, 1936, February 18, 1937, and April 6, 1937, revealed no change in the shadow. On August 27, 1937, the film was clear.

Case 13. As a freshman in the school of nursing, in the fall of 1934, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1936. Roentgen-ray films of the chest were clear until the spring of 1936, when there was evidence of disease in the right third interspace. In the summer of 1936 there was evidence of pleurisy at the right base, but no evidence of fluid was observed. In the fall of 1936 there was evidence of considerable thickening of the pleura over the right base and marked elevation of the right side of the diaphragm. In December 1938 she was still in school, and the film revealed no evidence of disease in either lung.

Of the 137 who became reactors while in school we know of the following who developed demonstrable lesions after graduation:

Case 14. This student entered the school of nursing in the fall of 1930 as a non-reactor to tuberculin. In March 1932 she reacted to tuberculin. Films in 1930, 1931, and 1932 revealed no evidence of disease. In December 1935 she had evidence of tuberculous lesions in the left upper lobe. There have been no significant symptoms, and she was working as a nurse in January 1939.

Case 15. This student entered the school of nursing in the fall of 1930 as a non-reactor to tuberculin. She became a reactor in 1932. Roentgen-ray films in 1930, 1932, and 1933 revealed no evidence of disease. In January 1938 she developed pain in the chest. Examination revealed evidence of disease involving the right lung from the apex to the third rib. There was also evidence of disease in the left lung at the level of the third interspace near the periphery. Tubercle bacilli were present in the sputum. She was admitted to a sanatorium, where artificial pneumothorax was instituted on the right side. She is still a patient in the sanatorium and has continued on artificial pneumothorax.

Case 16. In the fall of 1931 this student entered the school of nursing as a nonreactor. In the spring of 1933 she reacted to tuberculin. Roentgen-ray films in 1932, 1933, and April 1934 were clear. However, in February 1935 there was definite evidence of disease involving the left lung from the apex to the second rib. Artificial pneumothorax was instituted and this treatment has been continued to the present time.

In table 8 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized.

TABLE VIII

School of Nursing I

(Twelve Weeks' Tuberculosis Service)

48 with primary complexes on entrance
  a. Lesions while in school 1
  b. Lesions since graduation 1 } (4.2 per cent)
137 developed primary complexes while in school
  a. Lesions detected while in school 11
  b. Lesions since graduation 3 } (10.2 per cent)
0 developed primary complexes after graduation

In table 9 we have indicated the percentages of those who developed primary and clinical lesions in Schools IV and I. See table 9 for types of lesions.

TABLE IX

School of Nursing IV

(Six Weeks' Tuberculosis Service)

204 developed primary complexes while in school
  24 (11.8 per cent) location of lesions detected
  10 (4.9 per cent) primary foci only
  2 (1.0 per cent) pleural effusion only
  1 (0.5 per cent) effusion and primary focus
  11 (5.4 per cent) probable to definite clinical lesions

School of Nursing I

(Twelve Weeks' Tuberculosis Service)

137 developed primary complexes while in school
  14 (10.2 per cent) location of lesion detected
  4 (2.9 per cent) primary foci only
  2 (1.5 per cent) pleural effusion only
  1 (0.73 per cent) effusion and primary focus
  7 (5.1 per cent) probable to definite clinical lesions

School of Education

686 reactors
  3 (0.44 per cent) location of lesions detected
  1 (0.15 per cent) primary focus only
  2 (0.29 per cent) clinical lesions

COLLEGE OF EDUCATION

When this study began we saw the need for a control group of students for observation. We selected the College of Education because its students are of approximately the same age as those in the schools of nursing and have been reared in the same types of communities. The only essential difference is that students in the College of Education come in contact with

no more persons with tuberculosis than other members of the general population, whereas students in the schools of nursing may come in contact with tuberculous patients as a part of their work. In the College of Education we found 24.8 per cent of the students were reactors on entrance and 28.5 per cent on graduation (table 10). One sees that the percentage of tuber-

TABLE X

School	Number of Students	Per Cent Reactors Entrance	Per Cent Reactors Graduation	Per Cent of Non-Reactors* Who Became Reactors
Education	224	24.8	28.5	5.3
Nursing II	120	15.0	41.2	34.3
Nursing III	204	24.5	45.6	27.9
Nursing IV	550	30.0	67.1	53.0
Nursing I	226	21.2	81.8	77.0

* Increase in Tuberculin Reactors Among Students in a College of Education and in Four Schools of Nursing from Entrance to Graduation.

culin reactors on graduation from schools of nursing in general hospitals which do not have tuberculosis services is definitely higher than in the Col-

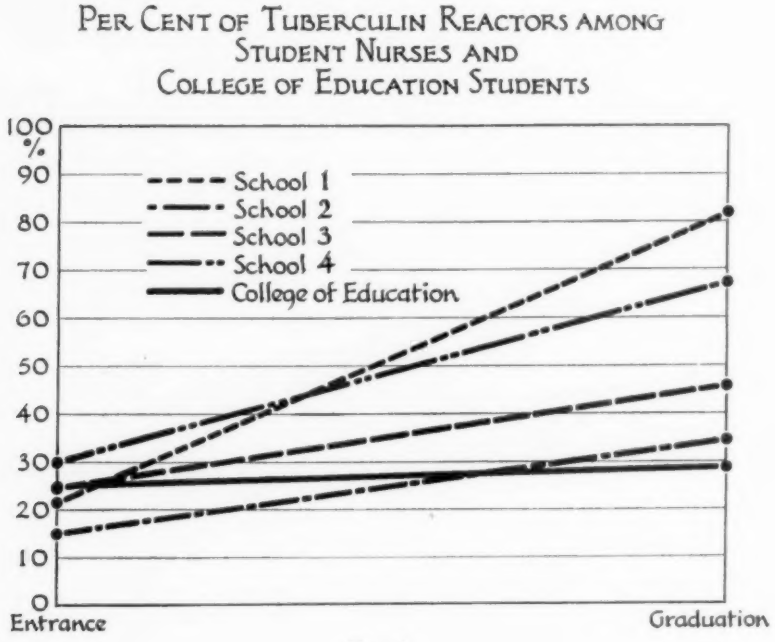

FIG. 1.

lege of Education. On the other hand, students in schools which have tuberculosis services have a much higher percentage of reactors on graduation than those from schools which have no tuberculosis service (figure 1). From the standpoint of demonstrable lesions there is also a sharp contrast

between the College of Education and the schools of nursing with a tuberculosis service. Among the students in the College of Education from 1932 to 1937 there was a total of 686 tuberculin reactors, and roentgen-ray film examination both on entrance and graduation revealed one primary parenchymal focus which later resolved and two which proved to have developed clinical disease.

Thus, we have found the tuberculosis problem among the students of nursing in four schools to be much greater than among the students in a College of Education in the same community. In our schools of nursing tuberculosis contracted while in school in the strict sense of the word has resulted in a number of girls discontinuing their training. It has caused much mental anguish among students and their relatives; it has caused long periods of illness; it has already caused death of a few; and it has caused much worry, chagrin, and embarrassment on the part of faculty members who have recognized the problem and feel a strong sense of responsibility for the health of the students of nursing.

A solution of this serious problem is of utmost importance and has been discussed by those who are desirous of eliminating this hazard to nurses in various parts of the world. Such factors as age, tuberculin reaction before entering the school of nursing, dosage of tubercle bacilli, and working hours have been considered important, but our experience has led us to believe that these factors have little to do either with causing the problem or solving it. Several workers have suggested the administration of BCG as the solution of this problem, and some have attempted it. Among 287 student nurses who became reactors following the administration of BCG Heimbeck found that eight later developed what he considered evidence of tuberculosis and one died. Among 107 others to whom he administered BCG, but who did not become reactors soon after, 22 developed what he reports as disease, and two died. Obviously, therefore, BCG did not prove a complete solution of this problem.

In our opinion there is only one true solution available at present, namely, the employment of a technic which will provide a barrier so efficient as to prevent the transmission of tubercle bacilli from patient to student. With this in mind two of our hospitals are already making serious attempts to prevent tubercle bacilli from entering the bodies of our students, both reactors and non-reactors to tuberculin. All members of the hospital personnel are examined adequately and periodically, in order to prevent our students from becoming infected by any person employed in the hospital. Patients entering all departments are examined for tuberculosis in contagious form, in order to avoid exposure of our students to unsuspected cases of tuberculosis. Each of these hospitals now has a tuberculosis service where rigid contagious disease technic is being practiced. If the technic now in use is not found entirely adequate, it must be intensified to such a degree as to solve our problem.

SUMMARY

1. A brief review of the literature reveals the fact that tuberculosis among student and graduate nurses is a serious problem in various parts of the world.

2. Our report consists of observations made in four schools of nursing since 1929. Students in a College of Education have been used as a control group.

3. In School II, where there is no tuberculosis service, 120 students were under observation. Eighteen were tuberculin reactors on entrance; 35 became reactors while in school, and 67 were graduated as non-reactors. Two of the students who entered as reactors developed pulmonary tuberculosis while in school; one of the 35 who became reactors had a primary focus in the lung parenchyma demonstrated by roentgen-ray film examination.

4. There was no tuberculosis service in School III. Here 204 students were observed, of whom 50 were reactors to tuberculin on entrance, 43 became reactors while in school, and 111 were graduated as non-reactors. None of those who reacted to the tuberculin test on entrance developed demonstrable lesions while in school. Of those who became reactors one developed a primary focus in the lung demonstrable by roentgen-ray film examination, and one developed bilateral clinical disease more than 18 months after she was known to be a reactor.

5. In School IV a six weeks' tuberculosis service was required of each student. Five hundred and fifty students were observed, of whom 165 reacted to tuberculin on entrance. Two hundred and four became reactors while in school, and 181 were graduated as non-reactors. Of the 165 who entered as reactors four developed demonstrable lesions while in school and two after the time of graduation. Of the 204 who became reactors as students 19 developed lesions demonstrable by roentgen-ray film or otherwise while in school, and five after the time of graduation (table 9).

6. In School I there was a 12 weeks' tuberculosis service during the first part of our period of observation. Here 226 students were observed, 48 of whom reacted to tuberculin on entrance, 137 of whom became reactors while in school, and 41 of whom were graduated as non-reactors. Among those who entered as reactors two developed lesions demonstrated by roentgen-ray film or otherwise while in school or after graduation. Of those who became reactors 14 developed demonstrable lesions while in school or after graduation (table 9).

7. In Schools II, III, and IV a questionnaire revealed the fact that some of the non-reactors on graduation had since become infected and a few had developed lesions demonstrated by roentgen-ray film or other methods.

8. We consider that every reactor to tuberculin has one or more primary tuberculosis complexes in the body. In this group the number who have developed demonstrable lesions located by roentgen-ray, etc., or who have

become ill from tuberculosis is sufficiently large to make the problem a serious one.

9. In the College of Education 24.8 per cent of the entering students reacted to tuberculin, whereas on graduation 28.5 per cent reacted. In a group of 686 reactors examined only three developed lesions in school which were demonstrated by roentgen-ray film examination.

10. A higher percentage of students reacted to tuberculin after taking a nursing course in a general hospital with no special tuberculosis service than in the College of Education. On the other hand, more students reacted to tuberculin after taking a course of nursing which requires a tuberculosis service than students in general hospitals which do not have such services. Obviously, the increase in percentage of reactors depends upon the amount of contact with contagious cases of tuberculosis.

11. In this entire study we have not seen a single student fall ill from miliary tuberculosis, tuberculous meningitis, or the so-called "infantile" type of tuberculosis.

12. Throughout this study no student developed tuberculosis as a non-reactor to tuberculin.

13. Our period of observation is brief for such a chronic disease. Therefore, we are of the opinion that more of the former students whom we have observed will fall ill from tuberculosis. This statement is based on the fact that annually new cases have been reported.

14. We do not believe that BCG has been proved sufficiently efficacious to solve this serious problem since evidence of tuberculosis has developed among some of the students so treated, as reported by Heimbeck and others.

15. In our opinion there is no method available, except a most rigid contagious disease technic, which provides a barrier and prevents the spread of tubercle bacilli from patient to student.

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ARTERIAL OXYGEN SATURATION IN CIRRHOSIS OF THE LIVER*

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The finding of a severe degree of oxygen unsaturation in the arterial blood of patients with cirrhosis of the liver has been reported by Snell.[1] Later, Keyes and Snell[2] studied a further series with oxygen dissociation curves, and found a small but significant shift in the curve from the accepted normal value. In this second series the oxygen unsaturation of the arterial blood was less marked than in the first series. From this work it was concluded that the hemoglobin in liver disease had properties somewhat different from normal.

Since there are few objective tests for measuring the disturbances of liver disease, Snell's results suggested to us that this test might furnish another index of these disturbances and might parallel changes in the clinical condition of the patients. Accordingly, arterial blood samples were tested on a series of patients being studied under various therapeutic régimes.

Case Material

The subjects comprised 34 patients with clinically diagnosed cirrhosis of the liver, on whom a total of 52 determinations of arterial blood oxygen were made. Twenty of the patients subsequently died, and in 13 of these the diagnosis was established by autopsy. The table presents the results of the tests, together with the patient's age in each case, and brief notes on the diagnosis. Wherever autopsy or liver biopsy was performed, that fact is noted.

Methods

Arterial blood was taken under oil from the brachial artery, with the patient recumbent. The blood was mixed with dry potassium oxalate under oil and the oxygen content determined immediately on duplicate 1 c.c. samples with the Van Slyke manometric apparatus. For the oxygen capacity, a further portion of the blood was agitated in room air for 10 minutes, and the determination was made likewise in duplicate. In both procedures the duplicate analyses were required to check within 0.2 vol. per cent.

To obtain a value for the oxygen combined with hemoglobin only, 0.2 vol. per cent was subtracted from the oxygen content and 0.5 vol. per cent from the capacity. Values in the table have been corrected in this manner.

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Results

It will be seen that the mean value of all determinations of arterial oxygen saturation, performed on the bloods of 34 patients, is 95.0 per cent, which is only 0.5 vol. per cent below the normal mean value on 12 normal young men, reported by Dill, Edwards, and Consolazio.[4] However, the mean age of our group is slightly over 50. On a group of healthy men over 60, Dill, Graybiel, Hurtado, and Taquini [3] found an average value of 92.3 per cent. Thus, considering average values for our entire group, no significant abnormalities can be noted.

Analyzing the individual cases, we find that in two determinations the oxygen saturation was below 92 per cent which may be considered unquestionably abnormal. However, both of these occurred in patient 17, who presented a special clinical picture. In addition to cirrhosis of the liver, this patient had a recurrent femoral thrombophlebitis with non-filarial elephantiasis. He had had several pulmonary infarcts. The roentgenograms of his chest showed increased markings in both lower lung fields. He complained of dyspnea on exertion, had clubbed fingers, and his pulmonary ventilation at complete rest was approximately 15 liters per minute. These pulmonary complications would seem to furnish adequate cause for his arterial anoxemia.

Although there is apparently no case in this series of severe arterial oxygen unsaturation due to liver disease, there are several instances in which a slight degree of unsaturation is found, i.e., in the range of 92 per cent to 94 per cent. The table shows that 10 determinations on 8 patients fall within this range. These include patients 2 and 19, who had repeated determinations in this range, and 5, 6, 7, 25, 28, and 34, with a single determination in the low range. However, two of these eight patients had frank pulmonary disease. Patient 2 had moderately severe chronic bronchitis and emphysema; patient 7 had a bilateral hydrothorax at the time his arterial oxygen saturation was low.

There remain, therefore, only seven determinations on six patients in which the arterial oxygen saturation was low and in which this fact cannot be explained by pulmonary disease. It should be noted, moreover, that of these six patients, one (number 5) was a man of 82 years, in whom a value of 92 per cent might not be considered abnormal in view of the findings of Dill et al.[3] on elderly men.

Our data have been analyzed to attempt to relate these few instances of lowered arterial saturation to some other feature of the disease in the patients. The finding is not related to the general severity of the liver disease, for it was not found in any of the seven patients who died of uncomplicated liver disease within three weeks of the test. This group includes patients 13, 15, 18, 26, 27, 32, and 33. Patient 33 deserves special mention because he showed an arterial oxygen saturation of 93.5 per cent early in the course of his illness, and 96.5 per cent later when he was moribund.

Summary of Measurements of Arterial Oxygen Saturation in 34 Patients with Cirrhosis of Liver

Patient No.	Age	Sex	O_2 Cont. Vol. %	O_2 Cap'y Vol. %	O_2 Sat'n %	Clinical Notes
1	62	M	16.7	17.6	95	Cirrhosis with massive ascites. Subsequently improved.
2	55	M	17.1	18.6	92	Moderately severe cirrhosis. Also emphysema and bronchitis.
			18.0	19.3	93.5	5 months later. Slightly improved.
3	41	F	10.4	10.7	97	Severe cirrhosis. Later proved by biopsy.
4	50	M	12.9	13.5	95.5	Cirrhosis plus thrombosis of portal vein. Autopsy.
5	82	M	13.8	15.0	92	Severe cirrhosis with ascites.
			14.3	14.8	96.5	8 months later. Improved.
			14.8	15.5	95.5	2 months later. Ascites-free. Autopsy 1 year later. Cirrhosis plus carcinoma of liver.
6	60	M	16.1	16.7	96.6	Cirrhosis with moderate ascites.
			16.0	17.1	93.5	9 months later. Unchanged.
7	48	M	16.3	16.9	96.5	Cirrhosis with ascites and intraperitoneal hemorrhage.
			14.5	15.5	93.5	6 months later. Also hydrothorax.
			13.1	13.6	96.5	2 months later. Condition poorer. Autopsy—Cirrhosis plus intraperitoneal hemorrhage.
8	39	M	17.4	18.0	96.5	Cirrhosis, club fingers.
9	46	M	17.3	17.8	97	Cirrhosis with recent ascites, tabes dorsalis. Autopsy.
10	63	M	13.0	13.7	95	Laennec's cirrhosis with ascites, and hypertensive disease.
			14.7	15.4	95.5	7 months later. Improved.
11	57	M	19.0	19.7	96.5	Cirrhosis plus thrombosis of portal vein. Autopsy.
12	26	F	14.7	15.2	97	Large fatty liver with early cirrhosis. Biopsy.
13	45	M	16.1	16.7	96.5	Cirrhosis. Rapidly downhill. Autopsy.
14	49	M	9.5	10.1	94	Cirrhosis, bleeding esophageal varices, portal vein thrombosis. Autopsy.
15	54	M	11.8	12.4	95	Cirrhosis. Rapidly failing.
16	60	M	15.9	16.7	95	Cirrhosis with moderate ascites.
			15.7	16.6	94.5	2 months later. Unchanged.
17	40	M	15.9	17.9	89	Cirrhosis of liver, femoral thrombophlebitis, pulmonary infarcts (see text).
			17.7	18.7	94	7 months later. Slightly improved.
			16.3	17.2	95	2 months later.
			16.5	17.1	96.5	3 days later.
			17.4	19.2	90.5	8 months later. Further improved.

Summary of Measurements of Arterial Oxygen Saturation in 34 Patients with Cirrhosis of Liver—*Continued*

Patient No.	Age	Sex	O_2 Cont. Vol. %	O_2 Cap'y Vol. %	O_2 Sat'n %	Clinical Notes
18	52	F	9.8	10.4	94	Cirrhosis. Rapidly downhill. Autopsy.
19	35	F	11.1	12.1	92	Severe cirrhosis with ascites.
			12.5	13.4	93.5	1 month later. Slightly improved.
20	63	M	15.8	16.7	94.5	Cirrhosis with recent ascites.
			16.8	17.8	94.5	5 months later. Improved.
21	42	M	12.5	12.9	97	Severe cirrhosis. Autopsy.
22	50	M	13.9	14.6	95	Cirrhosis with ascites.
23	49	M	15.9	16.6	96	Cirrhosis with ascites.
			13.5	14.3	94.5	9 months later. Less ascites.
24	45	F	18.5	19.4	95.5	Cirrhosis with severe peripheral neuritis.
25	36	F	11.0	11.9	92.5	Severe cirrhosis with ascites.
			11.3	12.2	94.5	1 week later. Unchanged.
26	52	F	17.8	18.2	98	Cirrhosis. Moribund.
27	31	F	12.2	12.7	96	Severe cirrhosis with ascites.
			16.8	17.5	96	4 months later. Unchanged. Autopsy 2 months later.
28	56	F	11.6	12.4	93.5	Severe cirrhosis with ascites.
29	59	M	13.1	13.7	95.5	Cirrhosis with ascites.
30	53	F	12.7	13.3	95.5	Cirrhosis with ascites, cerebral arteriosclerosis.
31	53	M	16.3	17.0	96	Cirrhosis, recently improved. Autopsy 1 year later.
32	60	F	9.4	9.7	96.5	Cirrhosis—rapidly failing.
33	38	M	18.9	20.2	93.5	Cirrhosis—rapidly failing.
			19.7	20.4	96.5	3 weeks later. Worse. Autopsy.
34	44	M	14.7	15.3	96	Severe cirrhosis with ascites. Autopsy.
Mean	50				95.0	

Likewise, attempts were made to correlate the few instances of arterial oxygen unsaturation with separate clinical features and laboratory tests: with jaundice, with severity of ascites, with peripheral neuritis, with level of serum albumin and bromsulphthalein retention. No correlation could be found with any of these features.

Summary and Conclusions

1. Fifty-two determinations of arterial oxygen saturation were made on 34 patients with cirrhosis of the liver.

2. Forty determinations on 31 patients were above 94 per cent, or within normal limits.

3. Twelve determinations on nine patients were below 94 per cent, the lowest being 89 per cent.

4. Of these nine patients, three had complicating pulmonary disease which adequately explains the anoxia. This group includes all instances of arterial saturation below 92 per cent.

5. The incidence of arterial oxygen unsaturation did not parallel other manifestations of the severity of the liver disease.

The initial observations in this work were made by Dr. James S. Mansfield and Dr. André Cournand, to whom grateful acknowledgment is made.

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A STUDY OF THE ACUTE LEUKOSES *

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MANY contributions have been made to the study of acute leukosis. Confusion still characterizes many features of this disease. We wish to present a clinico-pathologic study of 40 cases of acute leukosis observed in the Royal Victoria Hospital of Montreal in the past 20 years. We hope that this study will prove helpful in reëvaluating the wide diversity of opinions expressed.

We would define acute leukosis as a fatal disease of short duration, characterized by an untoward proliferation of primitive leukocytes in the hematopoietic tissue of the bone-marrow, lymph nodes, and spleen, with delivery of these cells to the peripheral blood in greater or lesser numbers. Infiltrations or metaplasia or both commonly appear in a wide variety of tissues and organs.

Hughes Bennett and Rudolph Virchow [38] first described leukemia in 1845. Virchow's original differentiation of lymphocytic leukocythemias and splenic leukocythemias is still widely applied, even in the classification of the acute leukoses.

Since the first case of acute leukosis was described by Von Friedriech [32] in 1857, further subdivision has been made on the basis of cell morphology. Some have attempted to elaborate a clinical picture peculiar to the cell type involved. The data available in this series of cases do not permit this differentiation.

INCIDENCE

In the past 20 years the incidence of acute leukosis was one case in 5960 admissions; 21 cases or 52.5 per cent were myeloblastic, 14 cases or 35 per cent were lymphoblastic, and 5 cases or 12.5 per cent were classified as monocytoid myeloblastic leukemia.

It is possible that the latter five cases were monoblastic. After a careful review of the material available, we were still unable to establish final conclusions in this matter. Although we have utilized supravital and other differential technics, we have failed to discover a single case of monoblastic leukosis in the past several years. As in the literature,[49] myeloblastic leukosis was the most common type.

In contradistinction to the usually reported greater incidence in males,[20, 37, 47, 49] 21 cases were females, and 19 were males.

Again in contradistinction to other reports,[20, 47, 48] the cases were almost equally distributed in the first four decades of life. After 40 the incidence decreased. The youngest case was two years of age and the oldest was 75.

* Read before the General Session of the American College of Physicians in Cleveland, Ohio, April 2, 1940.

It has been stated that acute leukosis rarely occurs after 25 years of age; approximately half of the cases in this series were over 25.

Heredity

In only two instances was there a history suggesting primary blood dyscrasias in other members of the family.

Clinical Features

The most common initial symptoms were in the following order: weakness, bleeding manifestations, anorexia, joint pains, unexplained fever, sore throat and general malaise. In only three instances did infection, and in only two instances did trauma apparently initiate the illness. Six cases were discovered because of bleeding following extraction of teeth or tonsillectomy.

A number of symptoms appeared frequently in the history of patients: weakness was present in 60 per cent, unexplained bleeding in 55 per cent, fever in 52.2 per cent, anorexia in 50 per cent, joint pains and bone pains in 47.5 per cent, vomiting in 32.5 per cent, loss of weight in 27.5 per cent, headache in 25 per cent, sore throat in 22.5 per cent, general malaise in 22.5 per cent, pallor in 20 per cent, glandular enlargement in 17.5 per cent, shortness of breath in 17.5 per cent.

A wide variety of other symptoms occurred either initially or during the course of the illness: frequent micturition and swollen testicles, deafness, abdominal pain, diarrhea, vertigo, visual disturbance, coma, drowsiness, convulsions, chills, palpitation, swelling of the salivary glands, chest pain, painful gums and sore mouth, dysphagia and dysarthria. Bleeding gums, epistaxis, purpura of skin and mucous membranes were the most common manifestations of bleeding; vaginal bleeding, hematuria, hematemesis, hemoptysis and melena occurred in several instances. These symptoms were present in all cell types of the disease.

Physical Signs

On admission to the Hospital general glandular enlargement was present in 24 cases, or 60 per cent. The cervical glands were more frequently involved than any other group, showing enlargement in 12 cases of lymphoblastic and 13 cases of myeloblastic leukosis. Axillary and inguinal glands were frequently involved.

The distribution and degree of glandular enlargement were essentially the same in all cell types of leukosis.

The Spleen: The spleen was slightly or moderately enlarged in 10 cases of lymphoblastic and 12 cases of myeloblastic leukosis, a total of 62.5 per cent. On admission the spleen was not palpable in four cases of lymphoblastic and in 11 cases of myeloblastic type of the disease. The spleen was not always palpable in the monocytoid myeloblastic group. Splenic enlargement could not be correlated with the predominating cell type.

The Liver: The liver was enlarged in 10 cases of lymphoblastic and nine cases of myeloblastic leukosis, a total of 47.5 per cent. It was not enlarged in four lymphoblastic and in 13 myeloblastic cases. The liver was not always enlarged in the monocytoid myeloblastic group. It will be noted that the liver was more frequently enlarged in the lymphoblastic than in the myeloblastic leukoses.

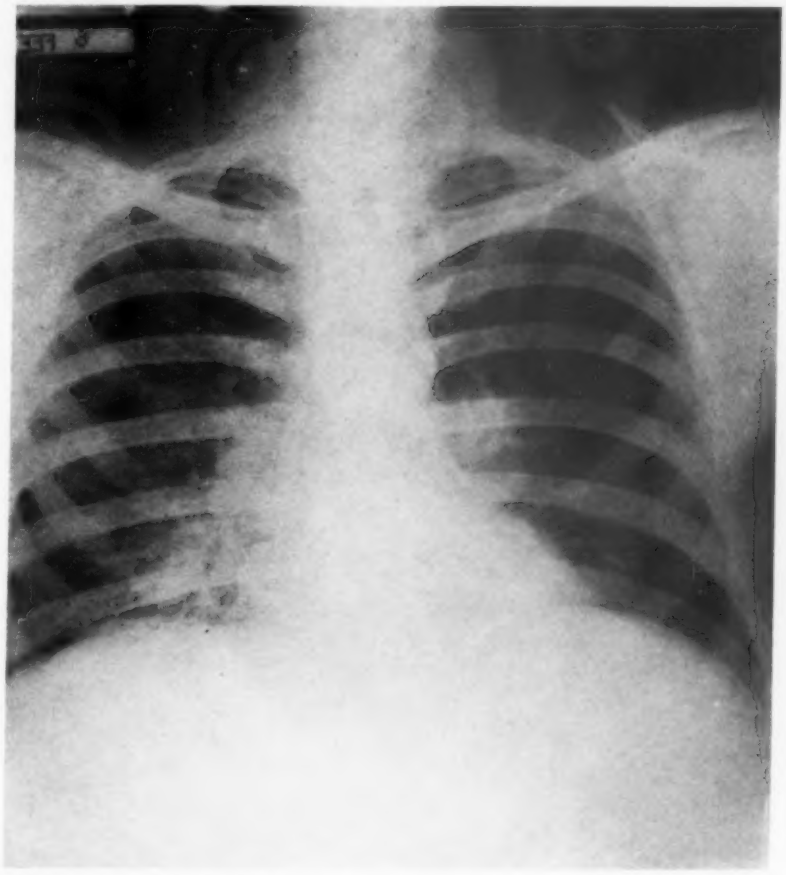

FIG. 1. Lymphoblastic leukosis. Leukemic involvement of mediastinum and lung. Bilateral hilar shadows with increased markings of lower right lung.

Bleeding Phenomena: During hospitalization bleeding occurred from one or several sources in the majority of cases of all cell types. The most common clinical sites of bleeding were the skin, mucous membranes, and retinae. Severe generalized hemorrhagic manifestations were not infrequent. Signs of visceral hemorrhage were present in many instances.

Skin Lesions: One case of lymphoblastic and four cases of myeloblastic leukosis showed leukemia cutis. The type of lesion differed in every instance.

Mucous Membranes: Swollen and ulcerated gums were present in 14 or 35 per cent of the cases, and showed no predilection for the cell type involved. Massive necrosis of the gum and jaw occurred in several cases.

Tonsils: These were markedly enlarged in nine cases and again there was no predilection for any cell type.

FIG. 2. Lymphoblastic leukosis. Leukemic involvement of fourth and fifth lumbar vertebrae; third sacral; ilium; ischium; pubis; hip joints; and the proximal femurs.

Pallor: When first seen, 37 of the cases or 92.4 per cent showed a greater or lesser degree of pallor; 67.5 per cent exhibited marked pallor. All types of the leukoses were involved.

Fever: Fever was present in every case. In three cases the fever resembled but was not typical of the Murchison-Pell-Ebstein type. All types of fever were encountered. Forty per cent of the cases developed complicat-

ing infections. Broncho-pneumonia was the most common and occurred in five cases.

Weight Loss: Weight loss occurred in 62.5 per cent of the cases.

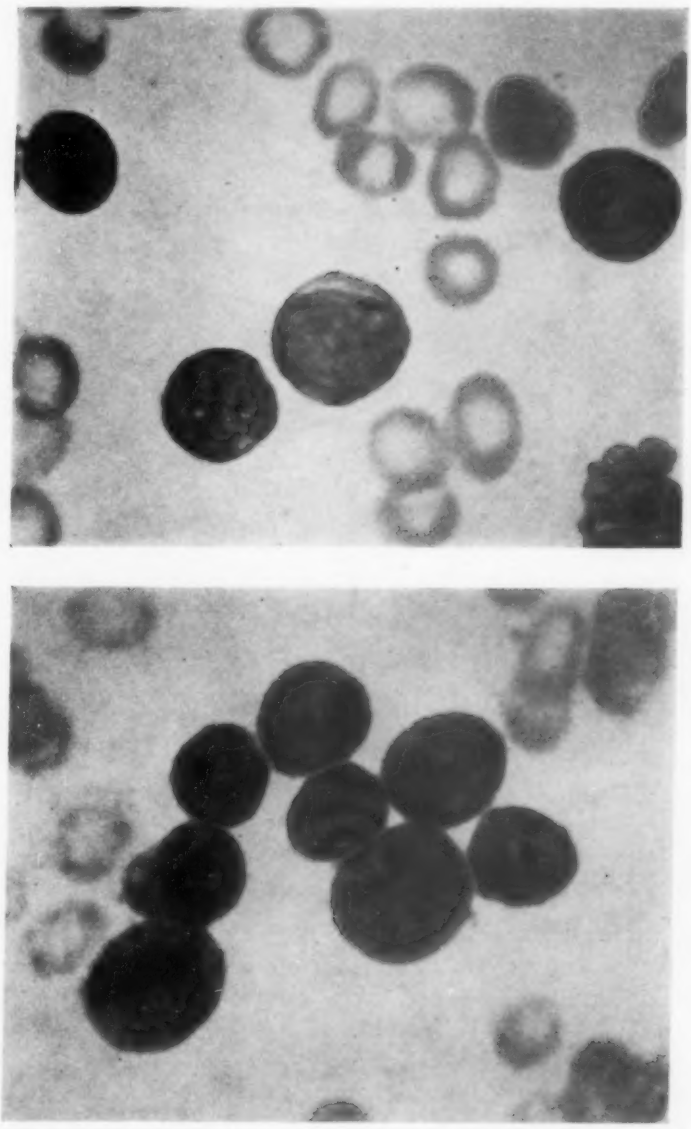

FIG. 3. Micromyeloblastic Leukosis. (*a*) *Above:* Micromyeloblasts in the peripheral blood. (*b*) *Below:* Cluster of micromyeloblasts in tissue aspirated after sternal bone marrow puncture.

Roentgen-rays of Lungs: Roentgen-rays of the chest were made in 22 cases; 15 showed thickened lung roots, and in 4 instances the lung parenchyma showed diffuse infiltration. We have been unable to find mention in

the literature of a comparably high incidence of lung changes on roentgen-ray examination.

Bone Involvement: That gross bone involvement may occur is illustrated by the presence of demonstrable roentgen-ray lesions of the tibia, femur, lumbar and sacral vertebrae, and pelvic bones in one of our cases. The high incidence of joint pain would suggest the desirability of further roentgen-ray and histologic study of joint tissues. Bone tenderness was a common sign.

Neurologic Involvement: This occurred in 22.5 per cent of cases, showed no predilection for the cell type involved and included cranial nerve palsies, evidence of cerebral, spinal cord and peripheral nerve lesions. Drowsiness, convulsions, and coma occurred in several cases.

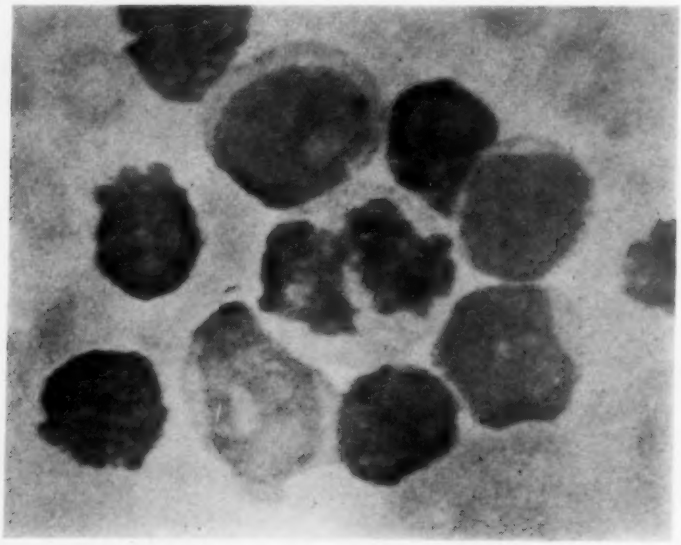

FIG. 4. Lymphoblastic Leukosis. Lymphoblasts in the peripheral blood. Note mitotic figures and Klein-Gumprecht shadows.

Miscellaneous Signs Noted: These included obstructive jaundice in two cases, extreme cyanosis, cardiac enlargement, Mickulicz' syndrome, and a tumor attached to the ribs.

Laboratory Findings: Elevated basal metabolic rates varied from plus 22 to plus 58 per cent. The blood non-protein nitrogen content was elevated in several cases. The highest value of 87 mg. per cent was associated with a uric acid of 20.2 mg. per cent, and at postmortem examination there was massive leukoblastic invasion of the kidney; the uric acid was elevated in 69 per cent of cases estimated.

Blood cultures, made from 14 cases, were sterile in every instance. Hematuria was present in 26 per cent. Fever could explain the other features found on urinalysis.

Duration of the Disease: The average duration was 10.2 weeks. The shortest duration was nine days; it occurred in a boy slightly over three years of age. The longest duration, eight and one-half months, was observed in a man aged 41 whose illness began with Brill's disease. The diagnosis of acute lymphoblastic leukosis was made three weeks before death. During the past 10 years there were twice as many cases of acute leukosis found in this hospital as were detected during the previous 15 years.

Mode of Death: We were particularly impressed with the mode of death in 28 or 70 per cent of the cases which was characterized by extreme weakness, circulatory collapse, rapid and labored respirations. Complicating infection was present in 20 per cent of the cases at the time of death. Terminal hemorrhage contributed to the circulatory collapse and death in eight cases, or 20 per cent. Five of these cases had subdural, subarachnoid, or cerebral hemorrhage.

Course: The course was universally downhill regardless of the treatment. Six cases developed coma. At least two cases became progressively worse after roentgen-ray treatment. All cases under observation for more than two weeks showed progressive enlargement of lymph glands, spleen and liver. Pallor and anemia increased with passage of time.

Hematology

On admission anemia was present in 39 or 97.5 per cent of cases. Almost one-third of the cases showed a moderate degree of anemia, i.e., between two and three million red blood cells and 40 to 60 per cent hemoglobin. Two-thirds showed a marked anemia, i.e., below two million red blood cells and below 40 per cent hemoglobin. In the majority of cases, the anemia was normochromic and normocytic; in a number of instances it was hyperchromic and macrocytic and in others hypochromic and microcytic. Nucleated red blood cells were present in 69.5 per cent and reticulocytosis in 57.5 per cent. As judged by the Van den Bergh reaction evidence of hemolysis was present in eight of the 10 cases studied. Thrombocytopenia was present in 84.4 per cent of the cases. In general the thrombocytopenia became more marked as the disease progressed.

The initial total white cell count was normal in six cases, leukopenic in two cases, and leukocythemic in 32 cases. The leukocythemic bloods varied from slightly above normal to 363,000 leukocytes. Spontaneous changes from a leukocythemic to a leukopenic phase occurred in two cases. In one case the white blood cell count rose spontaneously from 900 to 375,000. The other leukopenic case remained leukopenic. Most of the leukocythemic cases showed a tendency to progressive increase of the white blood cell count.

All leukoblasts were oxydase negative.

Several cases of myeloblastic leukosis were micromyeloblastic and usually careful search revealed the presence of occasional myelocytes. Auer bodies were present in the leukoblasts in two cases of the myeloblastic series and in one of the monocytoid cases. An occasional myelocyte was present in the

blood of the lymphoblastic leukoses. There was one case of lymphoblastic leukosarcoma.

Button or punch bone-marrow biopsy invariably showed the presence of a significant number of the responsible cell type.

Bleeding and Clotting Phenomena: In the three cases tested the blood prothrombin concentration was significantly decreased. In 15 cases the bleeding time was slightly to greatly prolonged. The clotting time was delayed in a number of instances. Rumple-Leeds test when performed was usually positive.

Effect of Therapy

In general, transfusions had no effect on the rapid progress of the anemia. In only a few instances was there any appreciable beneficial effect and this lasted only a few days. Transfusions had no definite effect on the white cell picture.

Deep Roentgen-ray Therapy: In several instances this was followed by a more marked thrombocytopenia and the initial appearance of bleeding. Roentgen-ray therapy was used in nine cases. In two instances the total leukocytes increased after therapy, and in two instances there was a marked increase of leukoblasts. In several instances roentgen-ray therapy was followed by a drop in the count, only to rise again several days after the discontinuation of the treatment. In not one case was there any lasting clinical or hematological benefit following roentgen-ray therapy. In several instances we believe this treatment hastened the lethal course of the disease. Radiation sickness occurred frequently after roentgen-ray therapy. Fowler's solution, benzol, and all other forms of therapy used had no appreciable effect.

Pathology

Postmortem studies were made in three cases of monocytoid myeloblastic, four cases of lymphoblastic, and eight cases of myeloblastic leukosis.

Grossly, regardless of the cell strain involved, hepatomegaly, splenomegaly, general glandular enlargement, hyperplastic bone-marrow and hemorrhagic manifestations were present in every case. In two cases enlargement of the retroperitoneal glands was greater than the glandular enlargement elsewhere. Diffuse hyperplastic metaplasia was present in the bone-marrow, lymph nodes, spleen and liver, in every case autopsied.

Leukemic infiltration of a wide variety of tissues and organs was the rule. The responsible cell strain in no way determined the tissues involved. The degree of infiltration in any given organ varied from case to case. Leukoblasts almost invariably jammed the radicles of the portal veins, the portal and periportal areas, and in two instances formed gross tumor nodules in the liver. Massive infiltration of the kidneys, sufficient to produce renal insufficiency, was present in one lymphoblastic and two myeloblastic cases. In two cases the enlargement of the spleen and liver was so marked (e.g.,

myeloblastic leukosis with a spleen of 1500 gm., and liver of 3030 gm.) that the possibility of a preëxisting chronic leukosis was suggested.

Extensive and diffuse hemorrhage involved in order of frequency the skin, mucous membranes, pericardium, stomach, retinae, peritoneum, renal tissue, brain and lungs. Although purpura of the skin was the most common single site of hemorrhage, simultaneous bleeding in a number of the viscera was far more frequent and extensive.

Hemorrhagic infarcts of the spleen, bilateral hydrothorax and bronchopneumonia were each present in 25 per cent of the cases. Secondary infections were present in isolated instances. In several cases there was myocardial injury, due to fatty degeneration, leukoblastic infiltration or fragmentation of muscle fibers. Exudative ulcerative stomatitis was present in one case of the monocytoid variety.

We were particularly impressed with the presence of non-inflammatory pulmonary edema in those cases without pulmonary infection, and with the degree of pulmonary edema in those cases developing pneumonia.

Frequently, leukocytes occluded the lumina of many small blood vessels. Perivascular hemorrhage often occurred in the vicinity of these vessels.

The hematopoietic tissues exhibited several features of interest pertinent to the mechanism of the anemia:

1. In several cases large areas of comparatively normal bone-marrow were found in which leukemic cell hyperplasia was minimal, yet the anemia was severe in these cases.

2. Evidence of increased red cell destruction was found in the bone-marrow, spleen and liver of every case. Internal hemorrhage may have partially conditioned this finding in some instances. In several cases, however, hemorrhage was negligible and yet there was a hyperplasia of clasmatocytes and Kupffer cells, which were loaded with pigment, red cell fragments, and whole red blood cells.

The exudate of the pneumonias consisted predominantly of leukemic cells. Purpura of the skin was invariably associated with much more extensive bleeding into the viscera.

The blood picture rarely indicated the degree or distribution of visceral infiltration. Frequently the tissue infiltration was more striking than would be anticipated from the blood picture and occasionally vice versa. In two instances a rapid decrease of the peripheral leukocyte count was associated with symptoms due to sudden deposition of leukemic cells in the viscera.

On study of histological sections it was frequently impossible to differentiate the particular cell strain involved, nor were there pathological features characteristic of a particular cell type.

Diagnosis

A careful clinical history and a thorough physical examination are of great importance in establishing the diagnosis. Because of the widespread

nature of the infiltrative process in this disease, symptoms and signs may appear referable to disturbed physiology in almost any organ in the body. Recently a number of authors have referred to certain aspects of this subject.[1-10, 12-15, 17-19, 21-24, 26-28, 30-36, 39-46, 49-51] When present, bleeding into the skin, or from mucous membranes, fever, diseased gums or pharynx, general glandular enlargement, a large liver or a large spleen suggest a thorough hematologic observation. The latter includes, in addition to regular routine studies, supravital studies, marrow biopsy, gland juice and gland core studies, and adrenalin contraction of the spleen. The grave anemia, thrombocytopenia, the white cell count and the differential count, as well as the study of the clotting mechanism, were all important in arriving at an accurate diagnosis. Greatest difficulty is encountered in the leukopenic form of the disease. In spite of the more accurate means available to investigate these cases, time, patience, and repeated study are often necessary before a definite diagnosis can be made. This is even more true in the leukopenic stage of the disease. The appearance of a few relatively mature cells in the peripheral blood aids greatly in establishing a diagnosis.

Differential Diagnosis

Leukemoid states should always be considered in the differential diagnosis of the acute leukosis. The disease must be differentiated from neoplasms with bone marrow metastases, severe infections, malignant neutropenia, pneumonia, tuberculosis, pertussis, rheumatic fever, infectious mononucleosis, aplastic anemia, thrombocytopenic purpura, scurvy, lymphoblastoma, some primary anemias of children, and last but not least from an acute exacerbation of a chronic leukosis.

Comment

In this study of the acute leukoses, including 15 autopsies, we have been unable to correlate the history, clinical signs, laboratory findings, or gross pathology with a specific cell type, in contradistinction to the reports of others.[20, 30]

Surface evidences of bleeding usually indicated greater hemorrhages into internal organs. All lymphatic glands were extensively involved, regardless of the cell type of the disease.

Occasionally a full blown disease was discovered after a trivial operation (e.g., tonsillectomy), a minor infection (e.g., an infected finger), or a moderate injury (e.g., blow on chest). We agree with others that there is insufficient evidence to conclude that these factors played any etiological rôle.[16, 52] We were impressed with the pan-systemic invasion and reaction. No true remission was observed in this group of cases.

Anemia was always present, and was generally very marked. The red blood cells showed degenerative and regenerative evidences. Nucleated red blood cells were abundant, reticulocytosis was prominent, and hemolytic ten-

dencies were common. Thrombocytopenia was a constant feature. Prothrombin concentration was reduced in the cases studied. Immature white blood cells were constantly present. There were very few leukopenic cases in this series.

Acute leukosis is a disorder of all hematopoietic tissue in which white cells, platelets, red blood cells, hemoglobin formation, the clotting mechanism, and the physiology of internal organs are affected. In a number of instances the clinical and pathologic data (i.e., the increased indirect bilirubin, the failure of multiple repeated transfusions to improve the anemia, the presence of an abundance of healthy marrow in several cases, and the almost universal histologic evidence of increased red cell destruction) suggested that a hemolytic process rather than myelophthisis may have played the dominant rôle in the production of the anemia.[29] Inasmuch as the etiology is unknown, we would support the hypothesis that a maturation factor abnormality may eventually explain the pathogenesis of acute leukosis.[11]

Conclusions

1. We do not believe that there is a clinico-pathologic picture which is characteristic of the cell type involved in acute leukoses.
2. No therapeutic measure influenced the course of the disease.

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CASE REPORTS

HEREDITARY ANGIONEUROTIC EDEMA *

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Angioneurotic edema is usually regarded as a peculiar and interesting condition, appearing suddenly as a subcutaneous, localized swelling on one or more parts of the body and disappearing gradually without leaving any discernible evidence of the reaction. It was first described in detail by Quincke,[1] in 1882, as "an acute circumscribed edema of the skin" to differentiate it from the well-known superficial whealing of urticaria, and given the name angioneurotic edema by Strübing,[2] three years later. It was believed by both these authors that the underlying mechanism responsible for this condition was a vasomotor disturbance of the blood vessels (angioneurosis) of the subcutaneous and submucosal tissues giving rise to increased capillary permeability and edema, but the factors that regulated and controlled this mechanism were not understood. In the past two decades this condition has come to be looked upon as a manifestation of allergy. Evidence has been accumulated to support the view that protein hypersensitiveness plays an important rôle in the causation of this disorder. Many reports of large series of cases have been published wherein protein skin tests, in some measure, have proved to be of diagnostic aid in determining the etiologic factors and yet it is in this type of allergy that the least satisfactory results are obtained.

Angioneurotic edema may be classified into three clinical types: (1) the acute or transient type, (2) the chronic or recurrent, and (3) the familial or hereditary type, with which this article is particularly concerned.

The *acute* type is characterized by localized, pale, indurated swellings surrounded by erythema varying in size and shape and occurring most frequently on the face, eyelids, lips and extremities, less often on other parts of the body. Rarely are the mucous membranes of the pharynx, glottis and larynx involved. It usually affects young adults, more often females than males. As a rule there is a history of only one or two attacks without subsequent recurrence. Protein skin tests sometimes help in determining the etiology but frequently the condition disappears without any known cause. A positive family history of allergy is elicited in only a small per cent of cases. In this type the prognosis is good.

The *chronic* type differs from the aforementioned in that attacks occur more frequently and the illness extends over a longer period of time. The areas involved are usually the same except for a greater tendency to affect the throat and larynx. Edema of the latter may give rise to alarming symptoms but rarely terminates fatally. Protein skin tests are more apt to be positive, and yet, here too an appreciable number of cases are found to be refractory to the great variety of allergens commonly used. Foci of infection, gastrointestinal disorders, psychogenic and endocrine disturbances have been demonstrated to be of etiologic

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significance. A positive family history of allergy is more often elicited and a history of other forms of allergy in the patient is more frequently obtained. Here, too, the prognosis is good.

The *hereditary* type is classified separately because it occurs in many members of a family and is transmitted from generation to generation, differing in this respect from the nonfamilial types just described. The line of inheritance seems to be direct with no skipping and reappearing and is apparently governed by a dominant Mendelian characteristic. Members not involved are less liable to transmit the disease. It occurs more frequently in males than in females and has its onset at any age. Once developed the tendency to recur remains throughout life. In some instances the same areas are involved but generally different parts of the body are affected. It is in this variety that edema of the glottis and larynx frequently occurs and terminates fatally. Osler,[3] who first emphasized the hereditary aspect of this condition, cites a family of 36 individuals through five generations in which 22 were affected, with one or possibly two deaths from sudden "edema glottidis." Ensor [4] reports a family of 80 persons in three generations with 33 afflicted members of whom 12 died of suffocation. Crowder and Crowder [5] in an article entitled "Five Generations of Angioneurotic Edema" published a family of 64 members in which 28 were affected and 15 died from the acute form of the disease. Fritz [6] cites eight afflicted members with five deaths and Blumer [7] reports six with four fatalities. Bulloch [8] in an analysis of 26 published reports assembled 170 cases occurring in families in from two to seven generations and in 36 instances (21.1 per cent) death occurred from edema of the glottis, indicating the high mortality rate of this condition. More recently Dunlap and Lemon [9] tabulated 21 families from the literature and added one of their own consisting of 24 members, six of whom died suddenly, two of undoubted glottic edema. From this brief review one is impressed with the seriousness of this type of edema as contrasted with the non-familial variety previously described.

The hereditary type is at times associated with visceral manifestations characterized by nausea, vomiting, abdominal colic and diarrhea which may simulate an acute surgical abdomen but which can usually be differentiated from it by the history of subcutaneous swellings on various parts of the body. In the absence of this history, however, the diagnosis is more difficult and operations have been performed for manifestations which later proved to be localized edema of the viscera.

In the reported cases where protein skin tests were done with some of the common allergens the results were invariably negative. In one member of the family herein discussed (case 2) a complete series of skin tests was performed with negative results. Keidel,[10] however, obtained a markedly positive reaction with an autogenous vaccine of *B. coli* obtained from the stool of a young girl with this disease, but the significance of the reaction is equivocal. The personal and family history in this variety does not usually reveal the presence of any other type of allergy.

Fortunately this type of edema is extremely rare. Rowe,[11] Tuft,[12] Hansel [13] and Bray [14] in discussing it quote instances from the literature but apparently have had no personal experience with it. Rackemann [15] also mentions this condition but reports no observations from his own clinic or practice and considers the incidence of such cases extremely rare. Menagh,[16] Fink and Gay,[17] and

Brown [18] omit it from their statistical studies on urticaria and angioneurotic edema. Because of the rarity of this condition and the serious aspects associated therewith another family is added to the literature with a detailed report of two of its six afflicted members.

Case Reports

Case 1. R. McC., a 19-year-old girl with a seven-year history of localized swellings on various parts of the body, was perfectly well up to 12 years of age, at which time she first observed swellings of the hands, feet and face lasting 12 to 24 hours and recurring every few months, but in no way incapacitating her. In the last two years the attacks became more frequent and more severe and would occasionally affect the face so that both eyes would be completely closed for a few days. At no time was there hoarseness, difficulty in swallowing, choking sensations or swelling of the tongue. Seldom would nausea, vomiting or abdominal pain accompany the illness.

There was no relation of the edema to the menstrual cycle or seasons of the year, nor was there any history of attacks following exposure to cold or heat. Emotional excitement, however, would occasionally precipitate an attack. It is interesting to note that a tonsillectomy was performed about the time of onset of the trouble. Diet, infections, drugs or contactants could not account for its appearance. The mother reports that protein skin tests were done with negative results. There was no history of urticaria, asthma, hay fever, eczema or migraine in the patient or in any known member of the family. All other data are irrelevant except for the familial history of angioneurotic edema. The mother, maternal grandmother and great-grandmother suffered with the same condition and one brother and sister were similarly affected. Since no reliable account concerning the other relatives was obtainable a genealogic table was not included in this report.

On January 22, 1936, the patient noticed a slight swelling of the right side of the neck and consulted a dentist. The following day she felt better, the swelling had somewhat subsided and at 6 p.m. she went to work in a cabaret restaurant where she was employed as a dancer and observed that the swelling was gradually becoming larger. Being much concerned she left earlier than usual and returned home at 9 o'clock, at which time both sides of the neck were involved. Within five minutes she gasped for air, rushed out to the street and pointed to her throat as the site of the trouble. Her face became swollen and cyanotic, the dyspnea more extreme and she was rushed to the hospital only two blocks away where she died while being carried to the emergency room. The intern who responded immediately to the call found her pulseless and frothing at the mouth and administered an intracardiac injection of epinephrine hydrochloride (1–1000), 1 c.c., without effect. She had died of asphyxia before tracheotomy could be performed.

Examination shortly after death revealed a milky-white indurated edema of half of the lower lip and extreme edema of the soft palate, uvula and pharyngeal muscles of the same serous appearance. The glottis was completely obstructed and would barely permit the passage of a fine probe under pressure. The tongue, cheeks, hard palate and epiglottis were not involved. The larynx was not examined and no autopsy obtained.

Case 2. Mrs. McC., 47 years of age, mother of the patient just described, was admitted to the allergy clinic 10 days later. She gave a history of angioneurotic edema of the upper and lower extremities and face since the age of nine with attacks occurring every few months in the early years and later more frequently. The throat was never involved. Only occasionally did she have vomiting and a bloated feeling in the abdomen.

Physical examination was essentially negative. A complete series of protein skin tests with the scratch and intradermal methods revealed negative results. She

was given elimination and trial diets without beneficial effect. During 18 months' observation she had 13 or 14 attacks, each lasting two or three days. The upper extremities were most often involved and at times the edema was so extensive as to produce a continuous brawny swelling from the mid-arm to the tips of the fingers. On one occasion after a slight trauma to the forehead the lids of both eyes became enormously swollen and the patient could not see. The swelling spread to the cheeks and upper lip and the facial expression was so distorted that she could not be recognized. In three days the condition returned to normal.

Blood studies carried out during an attack of severe edema showed the following: hemoglobin 87 per cent, red blood cells 4,340,000, white blood cells 8,700; band forms 8 per cent, segmented 59 per cent, eosinophiles 2 per cent, lymphocytes 28 per cent and monocytes 3 per cent. Total serum protein 6.98 mg. per 100 c.c., albumin 5.22, globulin 1.76; albumin-globulin ratio 2.96. Blood sugar 98.0, sodium chloride 458, cholesterol 164, cholesterol ester 83.0, calcium 10.3 and phosphorus 4.0 mg. per cent. The heterophile antibody reaction showed agglutination in normal dilutions.

Further studies of the serum protein made during and after attacks are recorded in table 1. These findings seem to show an increased albumin-globulin ratio in the attack. The test for urine concentration was normal and the Van Slyke index was 70 per cent maximum clearance. This patient refused to return to the clinic for further study and treatment and so far as we know her condition is unchanged.

TABLE I

Blood Serum Proteins*

Date	Condition	Total Serum Protein	Albumin	Globulin	A-G Ratio
3/27/36	In attack	6.98	5.22	1.76	2.96
3/30/36	End of attack	7.25	4.98	2.27	2.2
4/3/36	Free interval	6.91	4.54	2.37	1.9
5/4/36	Free interval	6.98	4.2	2.78	1.51
5/22/36	In attack	6.82	4.72	2.10	2.25
5/25/36	Attack subsided	6.98	4.41	2.57	1.72
6/1/36	Attack	6.71	4.81	1.9	2.53
2/17/37	End of severe attack	7.66	4.95	2.71	1.83
4/12/37	In attack	7.02	4.85	2.17	2.23

* All determinations were made from blood taken in the morning on an empty stomach.

It may be mentioned here that few of the reported deaths include autopsy findings. Griffith [19] treated a 34-year-old woman who died suddenly of laryngeal obstruction and necropsy revealed marked edema, tenseness and pallor of the larynx with only a small aperture present. Microscopic sections showed not only edema of the mucous membrane but also involvement of the submucosa, deeper connective tissue and muscles. Wason's report [20] of a 14-month-old child pronounced dead on arrival at the hospital, revealed marked edema of the pharynx and larynx with involvement of the lower respiratory tract. The microscopic picture of the pharynx was essentially one of edema involving all layers. The blood vessels and lymphatics were moderately dilated. The findings of Morris [21] were quite similar to the above. Obviously the edema in such cases must be extensive and deep to cause asphyxial death.

EMERGENCY TREATMENT

Since little progress has been made in the prevention of this type of edema it is important to stress the immediate treatment to be employed when the glottis

and larynx become affected. Depending on the severity of the attack one or more of the following measures should be employed: (1) administration of epinephrine hydrochloride (1:1000) subcutaneously or intravenously and if necessary around the periphery of the pharyngeal swelling, (2) passage of a fairly firm rubber tracheal catheter beyond the edematous area and (3) tracheotomy as a last resort in extreme cases. Time is an important factor, and in some instances minutes weigh the balance between life and death. Patients should be warned of these dangers and strongly urged to seek medical care at the slightest suspicion of swelling of the throat. They should also be advised to carry with them, at all times, a nebulizer containing epinephrine hydrochloride (1:100) and a hypodermic syringe of epinephrine (1:1000) for self-administration.

Comment

Because of the serious consequences attached to hereditary angioneurotic edema this condition must be recognized and differentiated clinically from the relatively benign non-familial variety commonly seen. This can easily be accomplished by careful questioning on the part of the physician as to whether or not other members of the family and their antecedents have been afflicted with the same disorder. One must think not only of urticaria, asthma, hay fever and the other allergies when dealing with angioneurotic edema but must always bear in mind the possibility of that unusual type which is transmitted from generation to generation to the exclusion of the other allergies. In this variety sensitization to foods, inhalants, drugs and bacteria does not seem to play an etiologic rôle but some evidence points to the possibility that physical agents and emotional stimuli act as exciting factors. In the two cases herein reported trauma was believed to have been responsible for an occasional attack and no other history could be elicited which would throw light on its etiology. Whatever the agent may be, it is reasonable to assume that it is the same for all affected members of a family. In this connection it should be noted that hay fever, in some instances, occurs in many members of a family and through several generations, in the absence of all other manifestations of allergy and due to specific hypersensitiveness to the same pollen antigen. Such a circumstance, to be sure, is not common and is explained on the basis of an unusually strong hereditary factor. It is generally believed that the more complete the inheritance, the greater the incidence of the same type of allergy; and so it may be with hereditary angioneurotic edema where the inheritance factor is most complete but where the causative agent is not definitely known. In this variety the edema is extensive and severe, with a predilection for the glottis and larynx and frequently causes death from asphyxia, while in the non-familial variety, where the hereditary influence is incomplete and at times apparently absent, the edema assumes a much milder course and rarely endangers the life of the patient.

Histamine has been recently employed with some success in the treatment of non-familial angioneurotic edema and is worthy of trial in the hereditary type.

Summary

Hereditary angioneurotic edema is discussed and differentiated from the acute and chronic varieties commonly seen. A family of six affected members in four generations is added to the literature with a report of two cases, one terminating fatally from edema of the glottis.

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TREATMENT OF UNDULANT FEVER WITH SULPHANILAMIDE; CASE REPORT *

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The use of sulphanilamide in the treatment of undulant fever has been recently advocated.[1, 2, 3, 4] In the case herein described, features other than the disappearance of fever seem to make it worthy of recording.

Case Report

C. R., a white male, aged 32 years, a department store executive, was first seen on May 14, 1938. He complained of chilly sensations, fever, sweats, and malaise. His

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family medical history was unimportant. In the past he had been free from major illnesses, with the exception of an attack of polyarthritis during childhood. This was thought to have been rheumatic fever, and bed rest had been enforced for eight weeks. From then on he had had no recurrence of the joint trouble, and no return of fever.

Forty-eight hours before being seen, the patient had become ill with headache, backache, and chilly sensations; elevation of temperature followed shortly, and he lost all desire for food. There were no cardio-respiratory or urinary symptoms and, with the exception of the anorexia, no gastrointestinal complaints. Sweating had occurred at intervals, and at times had been profuse. There was no pain in the joints. Until the onset of this illness, he had believed himself to be in good health.

Physical examination showed a robust young man who was not strikingly ill. The skin was warm and moist. The eyes, ears, and nose were negative to examination. The tongue was coated, and the pharynx slightly injected. There was a moderate amount of lymphoid tissue on the posterior pharyngeal wall. The neck was negative except for two moderately oversized nodes in the left anterior cervical chain. The lungs and heart showed no abnormalities. The heart rate was 90 to the minute, and the blood pressure was 132 mm. Hg systolic and 86 diastolic. Examination of the abdomen gave negative results. The extremities and reflexes were normal.

The temperature taken orally was 100.8° F. The white blood cells numbered 8,400, the red cells 4,560,000, and the hemoglobin was 84 per cent by the Sahli method. A differential count showed the white cells to be 58 per cent polymorphonuclear neutrophiles, 40 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles. Examination of the urine was negative.

The patient was thought to have grippe with pharyngitis, and the usual symptomatic measures were prescribed. Though during the next two days he improved symptomatically, his evening temperature continued at elevations of 101.0° to 102.0° F. At this time it was thought that the pharyngeal injection had increased, and he was given sulphanilamide, 45 grains daily, for the next three days. This, however, had no effect on the fever, thermometer readings continuing to fluctuate between 99.0° and 100.0° F. in the morning, and 101.5° and 103.0° F. in the evening. The drug was discontinued at the end of the three day period because of nausea and vertigo.

On the ninth day of the disease, agglutination tests for typhoid, paratyphoid A and B, melitensis, and tularemia were negative. An intradermal injection of a 1–100 dilution of *Brucella abortus* antigen failed to give a reaction. On the eleventh day another intradermal injection of a 1–5 dilution of the same material gave identical results. On the thirteenth day of the disease, another set of agglutination tests for typhoid, paratyphoid A and B, melitensis, and tularemia, performed in two different laboratories, gave negative results. Undiluted *Brucella abortus* antigen produced no reaction in 48 hours after injection within the skin. A blood culture was sterile, and a film of the chest negative. Several repetitions of blood counts and urine examinations revealed no essential changes from those originally done. Throughout a two-week period, the patient remained remarkably free of symptoms, with the exception of anorexia and sweats. His temperature continued at essentially the same level, readings in the morning being 99.0° F. to 100.0° F., and those in the evening being 101.5° F. to 103.0° F. Daily physical examinations failed to reveal any significant change.

On the fifteenth day of the disease, it was decided to give him another but more intense course of sulphanilamide. Accordingly, on the first day he received 60 grains of the drug, on the second day 80 grains, on the third day 90 grains, on the fourth day 80 grains, and on the fifth day 60 grains. Thereafter sulphanilamide was given, 45 grains daily for four days, and then stopped entirely. On the third day of drug administration, the nail beds and lips were cyanotic. On the fourth day of therapy, the skin at the site of the three previously negative intradermal tests showed the circumscribed inflammation of a positive reaction. The degree of reaction, more-

over, was in direct proportion to the concentration of antigen used, the inflammation at the site of the injected undiluted material being 4.5 cm. in diameter. Agglutination of the blood serum on this day against *Brucella abortus*, showed a positive test in a dilution of 1–640. On the fifth day of chemotherapy, the patient's temperature for the first time in three weeks dropped to normal in the morning, with an evening rise to 99.8° F. During the next two days it reached successively lower levels in the evening, and on the eighth day after starting the drug, it remained normal for 24 hours. From that time on he had no further fever. The skin reactions were maximum in intensity six days after starting the drug, and then faded gradually over a period of two to three weeks.

Comment

Two features of this man's illness seem worthy of mention. As a first consideration we have the appearance of positive intradermal reactions to *Brucella abortus* antigen following the administration of sulphanilamide to a patient with suspected undulant fever. This seems particularly significant since the three intracutaneous tests were interpreted as negative for six, eight and ten days, respectively, after injection, and became positive only after the patient had received maximum doses of sulphanilamide for four days. Moreover, appearing concomitantly with the positive skin tests, were serological agglutinins sufficient to give a positive test in a dilution of 1–640. The question naturally arises as to whether the antigen previously injected intradermally could not have given the positive agglutination. This seems unlikely, considering the height of the titer and the fact that previous agglutination tests, done following two of the intradermal injections, were negative. Welch, Wentworth, and Mickle [5] have recently reported upon determinations of the opsonocytophagic indices of persons with brucellosis before and after giving them sulphanilamide. They found phagocytosis to be increased after use of the drug and concluded that its administration may be of diagnostic aid in this disease. In three of the five cases they describe, moreover, agglutination tests which were negative before administration of the drug became positive after its use. It does not seem hypothetically impossible, therefore, that through the action of the drug, sufficient numbers of immune bodies may be produced to give a positive skin reaction and positive agglutination tests.

As a second consideration, we have the clinical recovery of a patient with apparent undulant fever, following the administration of sulphanilamide. The necessity for maximum dosage of the drug for successful treatment of the disease, as illustrated in this patient, is consistent with the experience of others. It is interesting that an earlier course of the drug in smaller doses and over a shorter period was without effect.

Summary

1. In a patient with suspected undulant fever, three *Brucella abortus* intradermal tests, which had been negative for six, eight and ten days respectively, showed a positive reaction after the administration of large amounts of sulphanilamide. Appearing together with the positive skin tests were positive agglutination tests, though they, too, had been negative before giving the drug.

2. A case of undulant fever showed clinical recovery, following the administration of large doses of sulphanilamide.

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FATAL "CONSTRICTIVE" PERICARDITIS DUE TO ISOLATED SUPPURATIVE PERICARDITIS THE RESULT OF INFECTED ABORTION; CASE REPORT *

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The object of this report is to describe a case of isolated suppurative pericarditis complicating a postabortive thrombophlebitis of the pelvic veins. Only one similar instance of suppurative pericarditis following an abortion has been found in a survey of the literature.[1] The pericarditis was evidently embolic in origin and developed about two weeks after the abortion. The patient then rapidly developed the symptoms of severe cardiac constriction † and died in circulatory failure within a period of eight weeks. An autopsy revealed extensive organization of the pericarditis and the formation of thick and rigid pericardial scar tissue.

Case Report

Clinical History: B. K., a white housewife, 28 years of age and the mother of three children, was admitted to University Hospitals on September 18, 1938 with complaints of severe dyspnea and edema of the lower extremities. Nine weeks before admission an allegedly criminal abortion was performed when she was one month pregnant. Following this procedure she had profuse vaginal bleeding for several days and then developed chills and fever together with a foul vaginal discharge. These subsided completely within two weeks but she failed to improve and remained in bed most of the time because of weakness and dyspnea. There was no abdominal pain. Five weeks before admission she began to complain of epigastric distress, nausea and frequent vomiting. Two weeks before admission she noticed swelling of the ankles for the first time. The shortness of breath and edema became progressively worse and she entered the hospital.

Her health prior to the present illness had been excellent.

Physical Examination: The temperature was 37.5° C., pulse 105–130, respirations 36 and blood pressure 100 mm. of Hg systolic and 80 diastolic. The patient was a well developed woman propped up in bed and showing extreme dyspnea. Although

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† The term constrictive is employed because of its widespread use in the literature. The term applies only in its figurative sense of holding fast or gripping, not necessarily in the sense of drawing together or rendering narrower or smaller. The lesion constrains the heart's diastolic expansion, but does not truly reduce the size of the heart in its systolic phase nor in its weight.

seriously ill she was cheerful and coöperative. The skin was cool and clammy and there was cyanosis of the face and mucous membranes. The neck veins were engorged and prominent. The lower extremities showed considerable edema which extended to the level of the sacrum.

The heart was questionably enlarged to the right, and there was marked suppression of the cardiac sounds. The pulse was rapid and regular but had a very small volume, at times was almost imperceptible, and was distinctly paradoxical. The bases of both lungs were dull to flat on percussion and showed diminished breath sounds and fremitus.

The abdomen was markedly distended and revealed shifting dullness as well as a distinct fluid wave. The liver was easily palpable and its right lower margin extended to the level of the umbilicus. The spleen was not palpable.

Laboratory Findings: The urine showed an average of 28 white blood cells per high power field. The red blood cell count was 3,100,000 with 60 per cent hemoglobin; the white blood cell count was 12,100 with 90 per cent polymorphonuclears. The Kline exclusion test was negative. The blood urea nitrogen was 6.5 mg. per 100 cubic centimeters and the blood sugar was 69 mg. per 100 cubic centimeters.

Roentgenologic examination of the chest revealed massive bilateral pleural effusion. An electrocardiographic tracing showed very low amplitude of the T-waves in the standard leads and a diphasic T-wave in Lead IV. These findings suggested myocardial damage.

Hospital Course: The patient was practically moribund on admission. She presented the picture of circulatory failure and cardiac compression, and the diagnosis of constrictive pericarditis was suggested. However, the etiology of this lesion was not clear.

Thoracentesis, performed on the evening of admission, removed 1 liter of clear yellow fluid from the right pleural cavity with considerable relief to the patient. The next morning her condition was about the same. A liter of clear fluid was removed from the left pleura. In the next few hours her cyanosis deepened and she became hard to arouse. Moist râles were heard throughout both lungs. The respirations became very shallow and the pulse was virtually imperceptible. Death occurred 26 hours after admission.

Postmortem Examination: Autopsy was performed 8 hours after death. Externally the body showed nothing unusual, except for a light brown, frothy discharge from the mouth. The skin was smooth and elastic and showed no petechiae or icterus.

The peritoneal cavity contained approximately 500 c.c. of clear, yellow, serous fluid, of specific gravity 1.005. The surfaces of the peritoneum were grayish-pink and hyperemic and showed no exudate. No fibrous adhesions were found in the pelvis.

Both leaves of the broad ligament were thickened and indurated, due to extensive thromboses of the uterine and ovarian plexuses of veins. Firm cords of thrombotic veins extended from the cornua of the uterus to the ovaries. The vessels varied from several millimeters to 1 cm. in diameter and their lumina contained impacted, friable, mottled grayish-red and white thrombi. Microscopic sections showed that these thrombi were composed of irregular or laminated strands of fibrin, masses of partly preserved erythrocytes and necrotic polymorphonuclear cells. In some veins there was slight organization of the thrombus at the site of intimal attachment. The vessel walls were well preserved although the adventitial and periadventitial connective tissue showed focal areas of lymphocytic infiltration.

The right main ovarian veins were completely occluded by thrombosis and formed a thick cord-like structure, extending up into the abdomen from the ovary. They terminated in a single large vein, 1.5 cm. in diameter, from whose distal end a thrombus projected into the lumen of the inferior vena cava (figure 1). The left main ovarian veins, the hypogastric veins and the uterine arteries contained no thrombi.

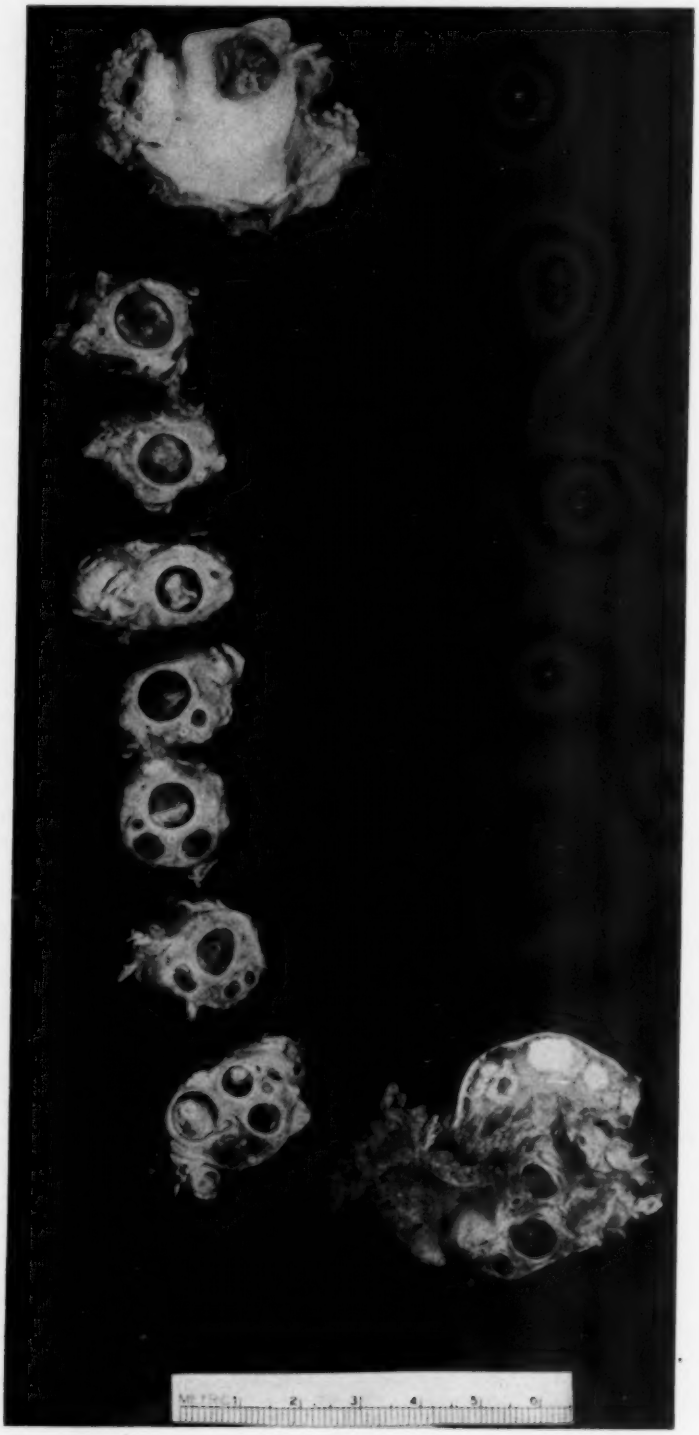

FIG. 1. Thrombosis of entire right main ovarian vein shown in serial cross sections from hilum of ovary to the inferior vena cava. Note thrombus projecting into the inferior vena cava.

The uterus was of normal size but was markedly retroverted. Several small thrombotic veins were found in the outer portion of myometrium of the fundus and body. The endometrial surface was dark red and smooth, except for a small portion of the fundus anteriorly which was covered by a thin, yellow, granular exudate. Microscopically this area showed a necrotic fibrinopurulent endometritis. No placental or decidual tissue was found. The Fallopian tubes and ovaries showed no significant gross or microscopic change. No corpus luteum was found.

The liver weighed 1450 grams and was the seat of severe passive hyperemia of nutmeg type. There were no areas of abscess formation and the portal veins were free of thrombi. Microscopically there was diffuse hyperemia of the intralobular sinusoidal network with severe compression necrosis of liver cells in the central zones, in the periphery of which there was a considerable polymorphonuclear cell infiltration. In the outer portions of the lobules the cells were loaded with small globules of fat. Special stains showed neither iron-bearing pigment nor any increase in connective tissue.

The spleen weighed 75 grams and was not noteworthy.

The entire gastrointestinal tract, the adrenals, the kidneys and the brain showed no significant gross or microscopic change. There was a mild subacute cystitis.

The thoracic organs occupied their usual positions. The right and left pleural cavities respectively contained approximately 850 c.c. and 250 c.c. of clear, yellow, serous fluid of specific gravity 1.008. There were extensive fibrous adhesions binding the pericardium to the mediastinal surfaces of the pleura.

The visceral and parietal layers of pericardium were markedly thickened and fibrous, and enclosed an organizing fibrinopurulent exudate (figure 2). There were

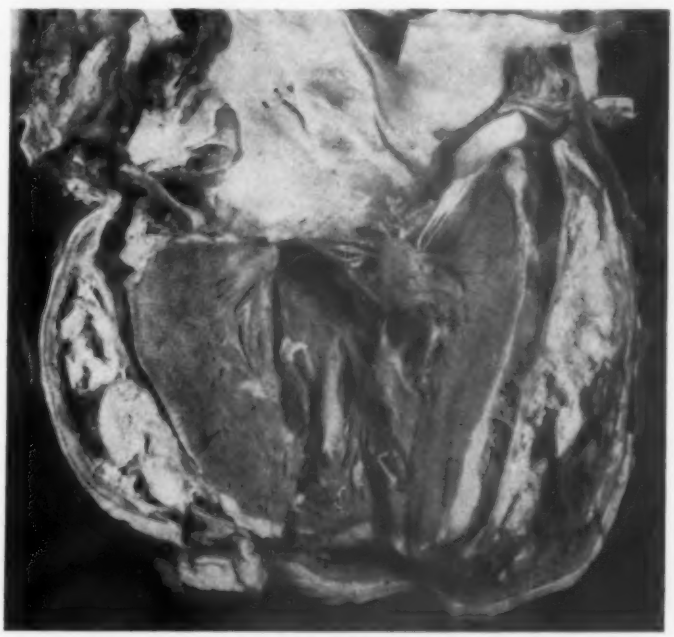

FIG. 2. Cicatrized fibrinopurulent pericarditis.

approximately 120 c.c. of yellowish-brown, purulent fluid, as well as pale yellow inspissated masses of fibrin in the pericardial sac. In some places, especially at the base of the heart and about the atria, the exudate was both organized and cicatrized

and the two layers of pericardium were fused and measured from 0.5 to 1.5 cm. in thickness. Microscopic sections of the fused portions revealed a dense mass of granulation tissue which was moderately well vascularized and showed focal infiltration of lymphocytes. Sections of the organizing fibrinopurulent exudate showed the formation of thick layers of young granulation tissue composed of actively proliferating fibroblasts and newly formed capillaries.

In situ, the heart appeared small. Its estimated weight was 275 grams. The myocardium of both ventricles was yellowish-brown and flabby. However, microscopically there were no areas of abscess formation or leukocytic infiltration. Sudan III stains revealed severe fatty degeneration of the muscle fibers. There were no mural thrombi within the atria. The valves showed no significant abnormality and the coronary arterial tree was not remarkable.

The lungs showed considerable hyperemia and edema, especially of the lower lobes. There were no foci of consolidation or abscess formation. The bronchial tree presented a moderately hyperemic, grayish-red mucosa and the lumina of the larger passages contained a slight amount of frothy, grayish-pink exudate.

The final pathologic diagnoses were: acute fibrinopurulent pericarditis with extensive organization; chronic constrictive pericarditis; thrombophlebitis of the uterine and ovarian plexuses of veins in the broad ligaments; thrombosis of the entire right main ovarian vein; subacute purulent endometritis; fatty degeneration of the myocardium; marked chronic passive hyperemia of the liver and spleen; pulmonary edema; hydrothorax (right 850 c.c.; left 250 c.c.); ascites (0.5 liter); subacute cystitis.

Bacteriology: Pure cultures of *Staphylococcus aureus hemolyticus* were recovered from the thrombi in the ovarian veins and from the pericardial exudate.

Comment

The sequence of events in this case is made plainly evident by the autopsy. Following an abortion, the patient developed a purulent endometritis. The inflammation extended into blood vessels in the wall of the uterus and led to an extensive thrombophlebitis of the pelvic veins. This evidently served as a source of invasion of the blood stream by septic emboli or bacteria which lodged in the pericardium, producing a suppurative inflammation. At autopsy no other site of embolic localization was found. The same organism, *Staphylococcus aureus hemolyticus,* was cultured from the pericardial exudate and from the thrombi in the ovarian veins.

When the patient was first studied clinically, she was in circulatory failure. The presence of distended peripheral veins and of an enlarged tender liver with ascites, together with suppression of the heart sounds and a paradoxical pulse led to a diagnosis of constrictive pericarditis. This lesion appeared to be related etiologically to the patient's abortion which occurred nine weeks previously, but the manner of association was not entirely clear. The autopsy revealed an extensive organizing fibrinopurulent pericarditis with partial obliteration of the pericardial sac and fusion of the visceral and parietal pericardium into one thick dense fibrous layer. This rigid tissue was responsible for the constriction which led to failure of the heart. The severity of the cardiac embarrassment was indicated anatomically by the marked pulmonary edema and hydrothorax, as well as by the passive hyperemia of the liver with central necrosis of the lobules and also ascites.

Suppurative pericarditis usually results from extension of infection in the lungs or mediastinum to the pericardium, either directly or by way of lymphatic vessels. It also occurs as a blood-borne infection, in association with a gener-

alized pyemia or a septicemia. In the present case the suppurative pericarditis was an isolated lesion which evidently had its source in a postabortive pelvic thrombophlebitis and was carried by way of the blood stream to the pericardium. The pericardial inflammation was quickly organized and within a period of several weeks sufficient scar tissue was formed to produce cardiac compression. Had the symptoms of constrictive pericarditis developed at a later time, the etiologic relation of the disease to a previous pelvic infection might easily have been overlooked. It appears probable that at least some cases of chronic constrictive pericarditis of obscure etiology originate in a similar manner as a result of metastasis from a pyogenic infection elsewhere in the body.

In retrospect the surgical implications of this case are important. The suppurative pericarditis developed within several weeks after the patient's abortion and was followed by the development of constrictive pericarditis. The symptoms were due to effects upon the heart of exudate and scar tissue, and not to the infection itself. In fact the pericardial lesion was silent until the mechanical effects of inflow stasis became manifest. Had a diagnosis of constrictive pericarditis been made early in the disease, drainage of the pericardial sac, by pericardiotomy, and removal of pericardial scar tissue might have been feasible. In Dujol's case [1] of suppurative pericarditis following an infected abortion the pericardial sac was aspirated and 200 c.c. of purulent fluid were removed. This was believed to be an important factor in the patient's recovery.

Summary

This report describes a case of suppurative pericarditis complicating a postabortive thrombophlebitis of the pelvic veins in a 28 year old woman. Shortly after abortion the patient rapidly developed the symptoms of severe compression of the heart and died in circulatory failure within a period of eight weeks. An autopsy revealed extensive thromboses of the uterine and ovarian veins and an isolated suppurative pericarditis which showed considerable organization. The resulting thick pericardial scar tissue was responsible for the fatal constriction of the heart. The metastatic nature of the pericarditis was clearly established by the recovery of the same organism, *Staphylococcus aureus hemolyticus,* from the thrombi in the ovarian veins as from the pericardial exudate.

REFERENCE

1. Dujol, G.: Péricardite purulente à staphylocoques au cours d'une infection post-abortum, Bull. Soc. d'obst. et de gynéc., 1929, xviii, 247.

EDITORIAL

THE ABSORPTION AND EXCRETION OF IRON

ALTHOUGH iron is an element vitally essential to all vertebrates, relatively little has been known regarding its exchange in the body. Iron unquestionably must be absorbed from the gastrointestinal tract, and there is good reason to believe that this occurs largely in the upper part of the small intestine. The details of its excretion are much less clear. Iron is normally present in the urine in only minute insignificant traces, and by exclusion it has been assumed that excretion occurs through the intestine. Some histological evidence has been advanced to support this view, but it is impossible to determine in this way whether iron which may be seen in the intestinal mucosa is being excreted or absorbed. It is also impossible to determine directly what portion of the iron in the feces may have been excreted and what has merely escaped absorption.

The total amount of iron in the body is small—normally only a little over four grams. Of this a large part, about 2.65 grams, is contained in the hemoglobin of the red cells. A small amount, about 0.3 gram, is present and functioning in other compounds in the tissues. Part is found in the myoglobin of the muscles, and part is known to be a constituent of certain oxidative enzymes present in all living cells. This iron is evidently essential to the life of the cells, as it never is abstracted for hemoglobin formation, even in the most severe anemias. In addition a larger and more variable amount, estimated at one-third to one-half of that in the hemoglobin, is stored in the tissues, chiefly in the spleen, liver and bone marrow, and is available for hemoglobin formation in case of need.

There is also a minute amount of non-hemoglobin iron in the plasma, from 60 to 150 micrograms per 100 c.c. This may be highly significant, nevertheless, since it is probably the form in which iron is transported in the body. This plasma iron is diminished in hypochromic anemias, but is increased in pernicious anemia.[1] In patients or animals with hypochromic anema it rises after the administration of absorbable iron preparations, and its rise is, within limits, proportional to the size of the dose. In untreated pernicious anemia, on the other hand, no such rise occurs.[2]

It is probable that the average life of the red cells is about 30 days. Hence the cells from about 175 c.c. of blood will be destroyed and replaced daily. These contain about 25 grams of hemoglobin, and 85 milligrams of iron is therefore liberated. It has long been known that the great bulk of this iron is retained in the body and is either stored or immediately used

[1] HEMMELER, G.: Serumeisen und Eisentherapie, Schweiz. med. Wchnschr., 1939, lxix, 316.

[2] MOORE, C. V., et al.: Studies in iron transportation and metabolism: IV. Observations on the absorption of iron from the gastrointestinal tract, Jr. Clin. Invest., 1939, xviii, 553–580.

for synthesis of new hemoglobin. It has been supposed that a significant amount is lost by excretion and has to be replaced from the food.

The need for iron varies with age and sex. It is greatest during the period of growth, both in young children and in adolescents; and in women who are menstruating as well as during pregnancy and lactation. Except in the presence of hemorrhage or active disease, it is only under these conditions that hypochromic anemia commonly develops. In normal adult males, in the absence of bleeding, the need is less. Recent balance studies show that this need is extremely small. Lintzel [3] maintained iron balance on an intake of only 1 mg. a day.

The experiments of McCance and Widdowson [4] cast doubt even on the possibility of the excretion of iron in significant amounts. They studied six normal individuals; first, during a control period in which they were in iron balance on an ordinary diet containing 7 mg. of iron daily. In a second period during which an additional 6 mg. of iron was given daily, by mouth, there was a corresponding increase in the iron in the feces; balance was maintained. During a third period, the extra iron, 7 mg. a day, was given by vein. Except for a slight but definite increase in the iron excreted in the urine during the first 20 minutes following the injection, this entire amount was retained. Since these individuals had been in iron balance and undoubtedly had adequate reserve stores of the metal, a substantial amount of this surplus iron should have been excreted if excretion plays any significant rôle in controlling iron metabolism.

More direct evidence as to this point has been furnished by the experiments of Whipple and his colleagues on dogs which have been depleted of iron and rendered anemic by repeated bleeding. By using iron salts containing radio-active iron, they were able to trace its distribution in the body tissues and excreta.[5] After injecting 100 to 250 mg. of radio-active iron as ferrous gluconate intravenously into dogs, whether anemic or plethoric, they found only very small amounts of this iron in the feces. During the first three to 15 days after the injection, appreciable amounts were found, in all from 2 per cent to 8 per cent of the injected iron. The daily excretion then fell to 50 to 400 micrograms, and this was maintained over an indefinite period. No more was excreted by the plethoric dog than by the anemic dog. They likewise conclude from these experiments that the dog excretes iron with difficulty, and that excretion can not play an important rôle in controlling iron metabolism.

Since, except in the disease hemochromatosis, iron is not stored in the tissues in unlimited quantities, some method of control must be exercised, and by exclusion this must be by varying the rate of absorption. There is

[3] Lintzel, W.: Zur Frage des Eisenstoffwechsels. V. Ueber den Eisenbedarf des Menschen, Ztschr. f. Biol., 1929, lxxxix, 342.

[4] McCance, R. A., and Widdowson, E. M.: The absorption and excretion of iron following oral and intravenous administration, Jr. Physiol., 1938, xliv, 148–154.

[5] Hahn, P. F., et al.: Radioactive iron and its excretion in urine, bile and feces, Jr. Exper. Med., 1939, lxx, 443–451.

considerable evidence that this is actually the case. In earlier experiments on anemic depleted dogs which had been maintained on a diet low in iron Whipple found that if food rich in iron, or ordinary iron salts in moderate doses were administered, a large part was absorbed and retained. Under favorable conditions, and with small doses (40 mg.), from 30 to 45 per cent of the iron was retained. This was followed within three to four days by a sharp increase in circulating hemoglobin. This increase, they believe, accurately measures the total amount of iron absorbed, since iron injected parenterally in such animals was totally utilized in forming new hemoglobin. In the normal dog, extra iron administered by mouth was not retained.

These conclusions have been confirmed by a duplication of these studies using radio-active iron compounds.[6, 7] When administered to anemic dogs substantial amounts were absorbed and retained. Within two to four hours after a single dose radio-active iron appeared in the plasma. It reached a maximum level after about six hours and then dropped off markedly, indicating that absorption is practically completed within 18 hours. The shape of this curve confirms the view that absorption occurs in the small intestine. Traces of radio-active iron were demonstrable in the red cells after four hours in some cases. After 24 hours substantial amounts were found, and substantially all the iron absorbed was incorporated in hemoglobin within four to seven days; and even within two to three days if hemoglobin production was active when the dose was given. The percentage of the administered iron which was absorbed varied considerably, and, in general, varied inversely with the size of the dose given. It was never complete, but ranged from 47 per cent of a 5 mg. dose to 3.2 per cent when 115 mg. were given.

When radio-active iron was administered to plethoric dogs only insignificant traces were absorbed—about 0.05 per cent.

Several observers,[8] however, have reported that when, in balance studies, very large doses of iron were administered to patients, or to normal individuals, considerably more iron was absorbed than could be accounted for by the hemoglobin formed. Presumably this is added to the body reserve stores. How far this plethora of iron can be pushed is not yet known.

It seems clear from these studies that there is no mechanism for controlling the excretion of iron, or even for effectively bringing it about under ordinary conditions, although in certain pathological states substantial amounts may be excreted in the bile. There is merely a wastage of small and relatively constant amounts of iron into the feces, probably not over

[6] HAHN, P. F., et al.: Radioactive iron and its metabolism in anemia. Its absorption, transportation and utilization, Jr. Exper. Med., 1939, lxix, 739–753.

[7] HAHN, P. F., et al.: The utilization of iron and the rapidity of hemoglobin formation in anemia due to blood loss, Jr. Exper. Med., 1940, lxxi, 731–736.

[8] FOWLER, W. M., and BARER, A. P.: The treatment of iron deficiency anemias, Jr. Am. Med. Assoc., 1939, cxii, 110.

1 mg. a day, which may be derived in part at least from desquamated epithelial cells.

On the other hand the amount of iron absorbed is adjusted, within limits, to the need of the body for iron. The mechanism by which control of this is brought about has not been demonstrated. It seems probable, however, as McCance and Widdowson suggested, that an important factor is the relative concentration of diffusible iron in the intestinal contents, and in the plasma and intestinal epithelium. In iron deficiency states in which the plasma iron is low, iron is readily absorbed. If the body is adequately supplied, the plasma iron is higher, and iron is not absorbed unless its concentration in the intestinal contents is raised to an unnaturally high level by giving large doses of medicinal iron. What part, if any, specific activities of the epithelial cells may play is not known. Precise knowledge of this mechanism must await further investigation.

P. W. C.

REVIEWS

The Building of a Nation's Health. By SIR GEORGE NEWMAN, G.B.E., K.C.B., M.D., F.R.C.P. 479 pages; 15 × 23 cm. MacMillan and Co., Limited, London, New York. 1939. Price, $6.00.

In the Second Annual Sedgwick Memorial Lecture in 1924 Dr. William Henry Welch referred to the great sanitary awakening, preceding the modern public health era, which began with the creation of the General Board of Health in England in 1848, and he said in part: ". . . every student of public health should read again and again the complete story as told so fascinatingly and authoritatively by Sir John Simon in his *English Sanitary Institutions.*" The student can now welcome a worthy continuation of this story that closed with the second edition of *English Sanitary Institutions* in 1897. Sir George Newman in *The Building of a Nation's Health* first sketches the backgrounds of the public health movement as presented by Sir John Simon and then describes the modern trends and achievements in official public health organizations on a nation-wide scale in Great Britain. The author of the present volume served as the first Chief Medical Officer of the Ministry of Health from 1919, when the Ministry was created, until 1935 and his evaluations of the many different kinds of national and local health programs have their roots in years of first-hand, practical experience.

The first chapter includes the historical events preceding the first national movement in public health in England: (1) the appointment of William Farr in 1839 as the medical statistician to the Registrar General; (2) Sir Edwin Chadwick's synoptical volume in 1842 of his Poor Law Commission report, "Sanitary Condition of the Labouring Population of Great Britain"; and (3) the enactment of the Public Health Act of 1848 inaugurating the General Board of Health. Although the Board ceased to exist as early as 1858 by reason of expiration of legislative provisions, it had laid the foundation for Parliamentary action in the interests of health programs. By 1869 Mr. Gladstone had appointed a Royal Sanitary Commission whose recommendations were incorporated in the Public Health Acts, first of 1871, second of 1872 and third of 1875. The Act of 1871 created the Local Government Board which functioned until the birth of the Ministry of Health in 1919.

In Chapter II there is a detailed account of the governance of English medicine by the State, of which the major event was probably the Medical Act of 1858 creating a *Medical Register* of qualified practitioners and providing for the maintenance of this Register by a "*General Council* of Medical Education and Registration of the United Kingdom" directly responsible to the Privy Council. This *General Council* continues today and consists of representatives of the Crown, of the Universities and of the Licensing Corporations. It is of interest to the American reader to note that the Council has become an agent of *Education* as well as an office of *Registration.* The Council reviews medical curricula and makes recommendations and one of its valuable collateral activities in the graduate field has been the registration of Diplomas in Public Health, a statutory duty imposed upon it by the Medical Act of 1886. The author entitles the third Chapter "New Spirit in English Medical Education" and in it he emphasizes the influence of Sir William Osler in all branches of medical education. The Earl of Athlane was appointed Chairman of a Post-Graduate Medical Committee by the Minister of Health (Dr. Addison) in 1921 and the work of the Committee reached fruition in the formal opening of the new London School of Hygiene and Tropical Medicine on July 18, 1929.

Sir George Newman in Chapter IV recounts the events leading up to the establishment in 1919 of the Ministry of Health, the principal health subjects within its

jurisdiction and its statutory functions among which medical research and coöperation with the medical profession occupy important places. The author in Chapter V attributes the final awakening of local authorities in public health in England to the success of the governance and medical leadership of the Ministry of Health, and in support of this he cites abounding documentary evidence. In Chapters VI, VII, VIII, IX, X, and XI the latest functions of national and local official health agencies pass in review before the reader—procedures in the fields of school medical service, including the rôles of the special school, physical education and recreation, maternity and infant hygiene, the nutrition of the people, and the welfare of the industrial worker.

In his Chapter (XII) "Health Insurance and Medical Research" and the succeeding one (XIII) "Whence and Whither," Sir George Newman details many telling arguments in favor of the leadership of the State in medical care as it exists in England. He declares the value of public health education in national and local programs is indisputable and states (p. 448): "No credit to preventive medicine stands higher in England than its service in the dissemination of knowledge on the control of disease, on the way of freedom from its thraldom, and on the more abundant life which full health of body and mind can bring to us all." The final chapter (XIV) is a glowing tribute to Sir Robert Laurie Morant, a devoted Civil Servant who contributed throughout his life to the advancement both of State education and public health. He succeeded in bringing the National Insurance Act within the scope of the Ministry of Health, the foundations of which he laid as its first Permanent Secretary during the 18 months before his death in 1920.

The Building of a Nation's Health is a splendid compendium of recent public health philosophy based primarily upon English experiences of the past, particularly since the turn of the century. Sir George Newman clearly traces the historical development of each health topic considered and the book, delightfully readable as it is, becomes a valuable reference volume for the student in public health who wishes a brief and authoritative account of the steps leading to our present attitudes and doctrines in public health administration. The frequent marginal, topical annotations in the book are convenient and helpful, and the chapter introductory quotations are especially well-chosen. The book contains five excellently produced portrait photographs and one of these entitled "Sir William Osler in His Library" is unusual. The format of the publication is pleasing.

W. H. F. W.

Fundamentals of Internal Medicine. By WALLACE MASON YATER, A.B., M.D., M.S., F.A.C.P. 1021 pages; 25 × 17 cm. D. Appleton-Century Company. 1940. Price, $9.00.

This book takes its place in the medical library between a compend and a detailed textbook on the subject. The author has accomplished his aim of presenting the minimal amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips.

Dr. Yater presents his material in a clear-cut, easily readable manner. Each section starts with an outline of the subjects to be discussed, followed by a brief introduction which takes into consideration physiology, important laboratory examinations, and symptoms distinctive of the system under discussion. The book is profusely illustrated, and the important points under each disease are set out in bold type. The sections are concluded with recommended texts for further reading.

The book seems a little out of balance in parts, as less space is devoted to discussion of diseases of the kidneys than to diseases of the eye and ear, two subjects rarely covered in a textbook of internal medicine.

The reviewer is favorably impressed with this book, and undoubtedly students of medicine and general practitioners will find much useful information provided it

is realized that the author makes no attempt to cover the field of internal medicine in detail.

W. K. W.

Immune-Blood Therapy of Tuberculosis. By JOSEPH HOLLÓS, M.D. 197 pages; 22 × 14.5 cm. Bruce Humphries, Inc. Boston. 1940. Price, $2.50.

Immune-Blood Therapy of Tuberculosis, by Dr. Joseph Hollós, takes up a mode of therapy which the author has been using for 30 years. To obtain immune-blood, rabbits are immunized with a culture of human and bovine tubercle bacilli. From the immunized animals blood is withdrawn from the vein, hemolized, freed from albumin, and diluted 1–100,000. This is the "original immune-blood."

This blood has a dual effect when injected or rubbed into the skin of hypersensitive tuberculous patients. In larger doses it produces many focal and constitutional symptoms through its lytic effect on tubercle bacilli in the patient, and in smaller doses relieves constitutional symptoms by its antitoxic effect.

Dr. Hollós' claims for this treatment are little short of miraculous and most of the volume consists of case reports personally followed by the author. The data are far too meagre to allow one to draw strictly objective conclusions. In the latter part of the book the author includes such diseases and symptoms as rheumatism, Graves' disease, dementia praecox, epilepsy, dysmenorrhea, leukorrhea, neurasthenia and various gastrointestinal symptoms as part of a picture of tuberculous intoxication in the absence of clinically active tuberculosis of the lung or other organs of the body. He does not hesitate to undertake the treatment of these conditions with "immune-blood therapy" and claims results equally as good as in the manifest tuberculous.

Dr. Hollós feels that the medical profession has been amiss in not accepting his therapy for tuberculosis but unfortunately the magnitude of the claims, the lack of control material and the lack of objectivity in presenting the subject make one hesitate before advocating any change in this point of view.

M. S. S.

The Newer Knowledge of Nutrition. By E. V. MCCOLLUM, ELSA ORENT-KEILES and HARRY G. DAY. Fifth Edition. 701 pages; 15 × 22 cm. Macmillan Co., New York. 1939. Price, $4.50.

The fifth edition follows the fourth by ten years. It is a nutritionist's *vade mecum* and no stranger to the majority of internists. It preserves the chronological approach, beginning with the history of nutrition, and progressing through bodily requirements to the modern concept of dietary essentials. A chapter each is given to carbohydrates, fats, and proteins. Much of McCollum's own work is included in the discussion of minerals in the diet. Vitamins are thoroughly dissected, and here the reader can find all those usually referred to as: "and many other factors," tracked down and specified in their proper relationship to the vitamin family alphabet.

Pica in animals is discussed along with the dietary habits of different ages and different parts of the world. Faddists are appropriately and rationally spanked. The effect of racial factors and modern transportation is elaborated upon. Diet in relation to teeth and caries is thoroughly considered, and a summary on the prevention of tooth decay is particularly interesting.

Throughout the book the perspective is broad, the judgments reasoned, and the conclusions logically based on facts previously mentioned. Several interesting tables are included concerning vitamins, and there are good bibliographic references at the end of each chapter.

C. A.

COLLEGE NEWS NOTES

POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

Winter and Spring of 1941

The Advisory Committee on Postgraduate Courses and the Committee on Educational Policy of the American College of Physicians announce the following courses, arranged through the generous coöperation of the directors and the institutions at which the courses will be given.

This is the fourth year of this activity by the College. The courses are offered especially for Fellows and Associates of the College, but where facilities are available, they are open to those preparing either to meet the requirements for membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College itself has assumed full responsibility for promotion, advertising, printing and registration as its contribution. This schedule of courses is announced after a complete survey of the needs and wishes of the College members. Due to a growing demand for courses at other periods of the year than just preceding the Annual Session, the College has initiated this year two courses in February and plans to extend the schedule to other seasons of the year in succeeding years, if the demand for such courses justifies this extension. The number of courses to be given as pre-meeting courses, just preceding the Twenty-fifth Annual Session at Boston, April 21–25, has been extended and the type of courses has been selected according to the recommendations of the membership.

Fees—The registration fee, regardless of the institution or course selected, is based on $20.00 for each week. One-half of the registration fee is payable at time of registration and the balance shall be paid not later than one week in advance of the opening of any course.

The College will record all registrations with the respective institutions offering courses and will directly reimburse those institutions for each student-physician at the specified fee. A matriculation card will be sent each registrant when his fee has been paid in full.

February Courses

St. Louis, Mo.

Dr. Harry L. Alexander, Director

Course No. 1. Allergy—Washington University School of Medicine

(2 weeks—February 10 to 22, 1941)

Rochester, Minn.

Dr. Edgar V. Allen, Director

Course No. 2. Gastro-enterology—Mayo Foundation of the University of Minnesota

(2 weeks—February 10 to 22, 1941)

Pre-Meeting Courses

Boston, Mass.

Dr. James H. Means, Director

Course No. 3. Advanced General Medicine—Harvard University Medical School
(3 weeks—March 31 to April 19, 1941)

Boston, Mass.

Dr. Paul D. White, Director

Course No. 4. Cardiology—Harvard University Medical School
(1 week—April 14 to 19, 1941)

Boston, Mass.

Dr. Chester S. Keefer, Director

Course No. 5. Gastro-enterology—Boston University School of Medicine
(1 week—April 7 to 12, 1941)

Ann Arbor, Mich.

Dr. Cyrus C. Sturgis, Director

Course No. 6. General Medicine—University of Michigan Medical School and University Hospital
(2 weeks—April 7 to 19, 1941)

New York, N. Y.

Dr. Robert A. Cooke, Director

Course No. 7. Allergy—The Roosevelt Hospital, Department of Allergy
(2 weeks—Dates yet to be determined)

Columbus, Ohio

Dr. Charles A. Doan, Director

Course No. 8. Hematologic Dyscrasias—Ohio State University College of Medicine
(1 week—April 14 to 19, 1941)

Philadelphia, Pa.

Dr. William D. Stroud, Director

Course No. 9. Cardiology—University of Pennsylvania Graduate School of Medicine
(2 weeks—April 7 to 19, 1941)

The two courses in Allergy have been correlated and essentially will cover the same subject matter. The course in General Medicine at the University of Michigan Medical School and the course in Hematology at the Ohio State University College of Medicine will be a repetition of the same courses given under the auspices of the College in the spring of 1940. The advanced course in General Medicine under the direction of Dr. James H. Means of Harvard University Medical School has been organized as a super-advanced course, covering a period of three weeks.

A one week's course in Cardiology and a one week's course in Gastro-enterology have been scheduled in Boston on alternate weeks, giving members who desire an opportunity to take both courses.

Detailed bulletins of the courses will be distributed to all members of the College as soon as ready.

New Life Membership

Dr. Charles R. Drake, F.A.C.P., Minneapolis, Minn., became a Life Member of the American College of Physicians on September 30, 1940.

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Books

Dr. George Bachmann, F.A.C.P., Atlanta, Ga.—"The Essentials of Physiology and Pharmacodynamics," 3rd edition;
Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn.—"Electrocardiographic Patterns—Their Diagnostic and Clinical Significance";
Dr. Edward G. Billings (Associate), Denver, Colo.—"A Handbook of Elementary Psychobiology and Psychiatry";
Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill.—"The Injured Back and Its Treatment";
Dr. Edgar Hull, F.A.C.P., New Orleans, La.—"Medical Nursing";
Dr. Hugh Alister McGuigan, F.A.C.P., Chicago, Ill.—"Applied Pharmacology";
Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla.—"Tuberculosis and Genius";
Dr. Wade W. Oliver, F.A.C.P., Brooklyn, N. Y.—"Fantasia";
Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore.—"A Textbook of Laboratory Diagnosis—With Clinical Applications for Practitioners and Students";
Dr. Harold E. B. Pardee, F.A.C.P., New York, N. Y.—"Nomenclature and Criteria for Diagnosis of Diseases of the Heart";
Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—"Diseases of the Gallbladder and Bile Ducts."

Reprints

Dr. George Bachmann, F.A.C.P., Atlanta, Ga.—16 reprints;
Dr. David M. Baltzan, F.A.C.P., Saskatoon, Sask.—1 reprint;
Dr. Harry S. Berman (Associate), Detroit, Mich.—1 reprint;
Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill.—2 reprints;
Dr. Jason E. Farber (Associate), Buffalo, N. Y.—4 reprints;
Dr. Wayne Gordon (Associate), Billings, Mont.—6 reprints;
Dr. Barnett Greenhouse (Associate), New Haven, Conn.—1 reprint;
Dr. M. Coleman Harris, F.A.C.P., New York, N. Y.—1 reprint;
Dr. John N. Hayes, F.A.C.P., Saranac Lake, N. Y.—9 reprints;
Dr. Merritt H. Stiles, F.A.C.P., Philadelphia, Pa.—3 reprints;
Dr. James J. Waring, F.A.C.P., Denver, Colo.—13 reprints;
Dr. Winthrop Wetherbee, Jr. (Associate), Boston, Mass.—1 reprint.

Twenty-Fifth Annual Session of the College

While the College celebrated its twenty-fifth anniversary in 1940, its Twenty-fifth Annual Session (no Annual Meeting was held during 1918) will be held in Boston, April 21–25, inclusive, 1941, with headquarters at the Hotel Statler.

The program for the morning Lectures and afternoon General Sessions is in charge of the President, Dr. James D. Bruce, Ann Arbor, Mich. Local arrangements and the program of Clinics, Panels and the Annual Banquet are under the General Chairman, Dr. William B. Breed, 264 Beacon Street, Boston. Local Committee

Chairmen are as follows:

Dr. Reginald Fitz—Committee on Clinics
Dr. Soma Weiss—Committee on Panel Discussions
Dr. F. Gorham Brigham—Committee on Entertainment
Dr. Howard B. Sprague—Committee on Auditorium
Dr. Earle M. Chapman—Committee on Transportation
Dr. Dwight O'Hara—Committee on Publicity

North Carolina Members Hold 1940 Regional Meeting

Fellows and Associates of the American College of Physicians of North Carolina held their Sixth Annual Regional Meeting at Chapel Hill, October 11–12, 1940, under the Governorship of Dr. Charles Hartwell Cocke. While this was the sixth annual get-together, it was only the second meeting in which the group had a scientific program. Dr. Paul F. Whitaker, F.A.C.P., Kinston, was Chairman of the Program Committee, and the scientific program was declared a most excellent one. Over 50 physicians out of a total of 82 Fellows and Associates in the State of North Carolina were in attendance. The scientific program occurred on Friday afternoon, October 11, and Saturday morning, October 12. On Friday evening a dinner was held at the Carolina Inn. Governor Cocke acted as Toastmaster and Dr. James D. Bruce, President of the College, delivered an address on "Recent Trends in Postgraduate Medical Education."

Friday Afternoon, October 11, 1940, 2:30 o'clock

(Auditorium, Medical Building)

Symposium on Cholecystic Disease

1. Etiology and Pathology of Cholecystic Disease. Dr. Edward J. Wannamaker, Charlotte, N. C.
2. Symptoms and Signs. Dr. Sidney F. LeBauer, Greensboro, N. C.
3. Roentgenologic Consideration. Dr. W. T. Rainey, Fayetteville, N. C.
4. Laboratory Consideration. Dr. E. B. Craven, Jr., Lexington, N. C.
5. Diagnosis (Correlation of History, Physical Examination, Laboratory and X-Ray Evidence). Dr. Wingate M. Johnson, Winston-Salem, N. C.
6. Differential Diagnosis. Dr. Walter R. Johnson, Asheville, N. C.
7. Management. Dr. Julian M. Ruffin, Durham, N. C.

Saturday Morning, October 12, 1940, 9:00 o'clock

1. A Report of an Unusual Case of Leukemia. Dr. K. P. Turrentine, Kinston, N. C.
2. The Psychoneuroses. Dr. Frederick R. Taylor, High Point, N. C.
3. Fatigue. Dr. James D. Bruce, Ann Arbor, Mich.
4. Recent Advances in Diseases of the Chest. Dr. S. M. Bittinger, Black Mountain, N. C.
5. Phytobezoars with Case Report. Dr. James H. McNeil, North Wilkesboro, N. C.

Regional Meeting—Illinois and Wisconsin Members

The Sixth Annual Regional Meeting of Illinois members (outside of Cook County) of the College was held at Rockford, Ill., Wednesday, October 16, 1940. Joined with the Illinois members were members of the College from Wisconsin. Dr. Samuel E. Munson, Governor for Southern Illinois, Springfield, and Dr. Elmer L.

Sevringhaus, Governor for Wisconsin, Madison, presided. Dr. Clarence H. Boswell, F.A.C.P., of Rockford, was Chairman of Arrangements.

The scientific program was as follows:

11:00 a.m.—Clinical Pathological Conference.
Dr. Harold D. Palmer, F.A.C.P., Pathologist, Rockford Hospital.

2:00 p.m.—"The Responsibility of the Internist to the Field of Industrial Medicine." Dr. Elston L. Belknap, F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wis.

"The Clinical Importance of Various 'Symptomless' Anomalies of the Gastrointestinal Tract." Dr. John A. Schindler (Associate), Monroe, Wis.

"Physical Aspects of Depressive Psychoses." Dr. Carroll W. Osgood, F.A.C.P., Wauwatosa, Wis.

The group were the guests of the Rockford Hospital at luncheon, which was combined with an American College of Physicians Conference with Dr. Ernest E. Irons, Chicago, Regent of the College and Chairman of the American Board of Internal Medicine, as the guest speaker, his subject being "The Work of the American Board of Internal Medicine."

Among other guests were Dr. James G. Carr, Second Vice President of the College, Dr. LeRoy H. Sloan, College Governor for northern Illinois, and Dr. N. S. Davis, III, F.A.C.P., all of Chicago.

At five o'clock in the afternoon a Reception, followed by dinner, was held at the Nelson Hotel. The meeting was enthusiastically attended by the Winnebago County Medical Society, as well as by approximately twenty-five Fellows and Associates of the College from Illinois and Wisconsin, making a total of approximately seventy-five.

Regional Dinner of Missouri Members

On the evening of October 3, marking the end of the Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, at Kansas City, a Dinner of the Fellows and Associates of the American College of Physicians was held under the Governorship of Dr. A. Comingo Griffith in honor of Dr. James G. Carr, Chicago, Second Vice President of the College. Twenty-three members were present. Dr. Carr made an interesting address and Dr. C. J. Barborka, F.A.C.P., Chicago, also gave an instructive talk. Thereafter there was general discussion concerning activities and objectives of the College. Members in attendance expressed the desire to have another meeting in the spring.

The annual Pottenger homecoming day was held in the gardens of the Sanatorium at Monrovia, Calif., September 22, 1940. Every year the "Graduates," or former patients, gather not only to renew their old acquaintances but to pay honor to Dr. Francis M. Pottenger. This year it was also to celebrate Dr. Pottenger's birthday (September 27). Personified in Earl Dunbar Meadows' poem as "The Mender of Broken Lives," written in 1932 when the subject was elected president of the American College of Physicians, Dr. Pottenger as founder and head of the Pottenger Sanatorium was honored by more than three hundred patients, former patients, and friends.

Dr. Horace K. Richardson, F.A.C.P., who has served for some time as Medical Director of the Austen Riggs Foundation, Stockbridge, Mass., recently resigned and has entered upon private practice of psychiatry at 11 E. Chase Street, Baltimore, Md.

Dr. Alfred B. Olsen, F.A.C.P., has accepted the position of psychiatrist to the Wabash Valley Sanitarium, LaFayette, Ind.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Health of the Football Official" before the Eastern Intercollegiate Football Association, at Hershey, Pa., September 7, 1940.

The 13th Annual Spring Clinical Conference of the Dallas Southern Clinical Society will be held March 17–20, 1941, in Dallas, Tex. Dr. Everett C. Fox, F.A.C.P., is president of this Society and Dr. W. Grady Reddick, F.A.C.P., is chairman of the Executive Committee. Among the guest speakers who will present papers at this meeting are Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., and Dr. Soma Weiss, F.A.C.P., Boston, Mass.

The Omaha Mid-West Clinical Society held its 8th annual assembly, October 28 to November 1, 1940. Among the guest speakers at the General Assemblies of this meeting were the following:

Dr. John Thomas Murphy, F.A.C.P., Toledo, Ohio—"X-Ray Treatment in Cancer of the Skin," "Cancer of the Cervix," and "Taking the 'X' Out of X-Ray Treatment";

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"Nephritis and Nephrosis," "The Changing Picture of Diabetes Mellitus," and "The Management of Hypertension";

Dr. Samuel Ayers, Jr., F.A.C.P., Los Angeles, Calif.—"The Problem of Acne and Seborrheal Conditions" and "Pyogenic Dermatoses—Diagnosis and Treatment";

Dr. Horton Ryan Casparis, F.A.C.P., Nashville, Tenn.—"Gastro-Intestinal Allergy of Infants and Children" and "Behavior Problems in Children";

Dr. Wendell Stanley Muncie (Associate), Baltimore, Md.—"The General Practioner's Stake in Psychiatric Therapy" and "Chronic Fatigue—Differential Diagnosis and Treatment";

Dr. George Herrmann, F.A.C.P., Galveston, Tex.—"The Clinical Study of Patients" and "Common Cardiac Emergencies and Their Management."

The following were among those who were Leaders of the Round Table Discussions:

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"The Elderly Diabetic";

Dr. Horton Ryan Casparis, F.A.C.P., Nashville, Tenn.—"Causes of Convulsive Seizures in Childhood";

Dr. Wendell Stanley Muncie (Associate), Baltimore, Md.—"Childhood Behavior Problems";

Dr. George Herrmann, F.A.C.P., Galveston, Tex.—"Pulmonary or Coronary Thrombosis???—Treatment."

Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Mich., and Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., were among those who presented a symposium on "The Anemias."

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., recently addressed the Academy of Medicine of Cleveland, Ohio, on "Present Status of Serum Therapy and Chemotherapy in the Treatment of Pneumonia."

Among the guest speakers at the 90th annual meeting of the Medical Society of the State of Pennsylvania, which was held in Philadelphia September 30 to October 3, 1940, were:

Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, Ohio—"Recent Advances in Vitamin Therapy";

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn.—"Hydatid Disease in North America."

The American Public Health Association held its 69th annual meeting in Detroit, Mich., October 6–11, 1940. Among the guest speakers at this meeting were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Some Important Factors in the Etiology of the Anemias";

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.—"An Assessment of the Nutrition of a Rural Population in Tennessee";

Dr. Julius H. Hess, F.A.C.P., Chicago, Ill.—"Essentials in the Care of Premature Infants";

Dr. George Baehr, F.A.C.P., New York, N. Y.—"Public Health Importance of the Intravenous Drip Method for Treatment of Syphilis."

Dr. Thomas Parran, F.A.C.P., Surgeon General, U. S. Public Health Service, presided at a special afternoon session on "The Control of Venereal Diseases in a National Defense Program." The speakers at this special session included Major General James C. Magee, F.A.C.P. (MC), USA, Surgeon General, U. S. Army, and Rear Admiral Ross T. McIntire, F.A.C.P. (MC), USN, Surgeon General, U. S. Navy.

Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., was installed as president of the Association and spoke on "Public Health in National Defense."

At a meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association in St. Paul, Minn., October 2–4, 1940, Dr. John H. Skavlem, F.A.C.P., Cincinnati, Ohio, presided at a roentgen-ray conference. Among those who presented papers at this meeting were:

Dr. Bruce H. Douglas, F.A.C.P., Detroit, Mich.—"The 4×5 Film in Case Finding";

Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill.—"Relative Usefulness of 35 Mm. Films in Case Finding."

Dr. George Argale Harrop, F.A.C.P., Princeton, N. J., was one of the speakers at a seminar sponsored by the Jefferson County (Ala.) Medical Society in Birmingham, September 16–17, 1940.

The Polk County (Iowa) Medical Society opened a series of postgraduate programs in Des Moines, September 18, 1940. Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., was one of the speakers at this opening meeting. His subject was "Food in the Practice of Medicine."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., spoke on the "Relation of Physiology to Modern Medicine" at another of these postgraduate programs on November 20.

This society has announced that Dr. David P. Barr, F.A.C.P., St. Louis, Mo., will speak on "The Making of a Diagnosis" on March 19, 1941, and Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., will speak on "Endocrinology in General Practice" on May 21, 1941.

Dr. Arthur C. DeGraff, F.A.C.P., New York, N. Y., addressed a meeting of the Academy of Medicine of Northern New Jersey in Newark, October 17, on "The Present Status of Digitalis Therapy."

Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., addressed a meeting of the Bergen County (N. J.) Medical Society on "Follow-up Work in Tuberculin Testing Surveys" at Bergen Pines, October 8, 1940.

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., was recently made an honorary member of the Argentine League Against Rheumatism.

Duke University School of Medicine and Duke Hospital, Durham, N. C., presented a symposium on diseases of metabolism and of the blood-forming organs, October 31 to November 2, 1940. Among the guest speakers were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Hemorrhagic Diseases";
Dr. Claude E. Forkner, F.A.C.P., New York, N. Y.—"The Leukemias";
Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass.—"Diabetes and Its Treatment";
Dr. Eugene F. DuBois, F.A.C.P., New York, N. Y.—"Clinical Application and Interpretation of the Basal Metabolic Rate";
Dr. George R. Minot, F.A.C.P., Boston, Mass.—"Some Aspects of the Etiology, Diagnosis, and Treatment of Iron Deficiency Anemias and Pernicious Anemia";
Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa.—"The Nature of Obesity, Its Prevention and Cure";
Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"What Is Hyperinsulinism?"

Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, Ohio, presided at a symposium on vitamin deficiencies at the semi-annual meeting of the Ohio State Hospital Physicians' Association held in Cincinnati, October 3–4, 1940.

Dr. Edgar V. Allen, F.A.C.P., College Governor for Minnesota, Rochester, addressed the Mahoning County (Ohio) Medical Society on "Peripheral Circulation" at their meeting in Youngstown, October 22, 1940.

Dr. Ferdinand C. Helwig, F.A.C.P., Kansas City, Mo., recently addressed the Tulsa County (Okla.) Medical Society on "Clinical and Experimental Studies of Coronary Disease with Special Emphasis on Trauma," at Tulsa.

Dr. Wann Langston, F.A.C.P., Oklahoma City, Okla., spoke on "Blood Dyscrasias" at a recent meeting of the Southern Oklahoma Medical Association in Shawnee.

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., was one of the speakers at the 10th annual fall clinical conference of the Oklahoma City Clinical Society held in Oklahoma City, October 28–31, 1940.

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, recently addressed a meeting of the Washington County Medical Society, held in Washington, Pa., on "The Problem of Ventricular Fibrillation and Cardiac Resuscitation."

Dr. Harvey G. Beck, F.A.C.P., Baltimore, Md., addressed the Lawrence County Medical Society at their recent meeting in New Castle, Pa. His subject was "Chronic Illness Resulting from Carbon Monoxide."

The Association of Military Surgeons of the United States held its 48th annual meeting in Cleveland, Ohio, October 10–12, 1940, under the presidency of Major General Charles R. Reynolds, F.A.C.P. (MC), USA, Retired, Harrisburg, Pa. Among the speakers at this meeting were:

Rear Admiral Ross T. McIntire, F.A.C.P. (MC), USN, Surgeon General, U. S. Navy,—"Selection of Men Adapted for Special Fields";

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—"Chemotherapeutic Developments Since the Last War";

Dr. Ernest P. McCullagh, F.A.C.P., Cleveland, Ohio—"Differential Diagnosis of Neurocirculatory Asthenia (Soldier's Heart) and Results in 152 Denervations of the Adrenal Glands in Treatment of Neurocirculatory Asthenia."

The Medical Society of the District of Columbia held its annual scientific assembly in Washington, October 15–17, 1940. The subject of this assembly was cardiovascular renal diseases. Among those who spoke at this meeting were:

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md.—"Some Interesting Electrocardiographic Interpretations";

Dr. Walter A. Bloedorn, F.A.C.P., Washington, D. C.—"Recognition and Treatment of the Various Forms of Pericarditis";

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.—"Diseases of the Aorta";

Dr. George Louis Weller, Jr., F.A.C.P., Washington, D. C.—"Surgical Shock and Circulatory Failure";

Dr. Thomas S. Lee, F.A.C.P., Washington, D. C.—"Hypertensive Heart Disease";

Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa.—"Renal Involvement in Hypertensive Vascular Disease";

Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md.—"Cardiac Aspects of Chronic Nephritis";

Dr. Howard B. Sprague, F.A.C.P., Boston, Mass.—"Clinical and Electrocardiographic Findings in the Aging Heart";

Dr. James Edwin Wood, Jr., F.A.C.P., Charlottesville, Va.—"Diagnosis and Treatment of Cardiac Arrhythmias";

Dr. James Alexander Lyon, F.A.C.P., Washington, D. C.—"Failure of the Left and Right Sides of the Heart";

Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—"Recognition and Management of Cardiac Neurosis";

Dr. Edwin Cowles Andrus, F.A.C.P., Baltimore, Md.—"Acute Coronary Thrombosis";

Dr. Irving Sherwood Wright, F.A.C.P., New York, N. Y.—"Diagnosis and Conservative Treatment of Peripheral Vascular Diseases."

Dr. Samuel F. Rosen, F.A.C.P., Savannah, Ga., spoke on "Occupational Dermatoses" at the 3rd annual meeting of the Georgia Association of Industrial Surgeons, held in Atlanta, September 25, 1940.

Dr. John H. Musser, F.A.C.P., New Orleans, La., has been appointed president of the Louisiana State Board of Health to serve on a part time basis until January, during the reorganization of the board.

The University of Minnesota Medical School, Minneapolis, has announced that Dr. Arthur C. Kerkhof (Associate) and Dr. James B. Carey, F.A.C.P., have been promoted to Clinical Associate Professors of Medicine.

Dr. Louis E. Viko, F.A.C.P., College Governor for Utah, Salt Lake City, spoke on "Etiology and Treatment of Hypertension," and Dr. Kenneth S. Davis, F.A.C.P., Los Angeles, Calif., spoke on "Limitation and Evaluation of the X-Ray in the Diagnosis of Disease of the Gallbladder" at the 37th annual meeting of the Nevada State Medical Association, held in Las Vegas, October 10–12, 1940.

Dr. Harry Beckett Lang, F.A.C.P., Brentwood, N. Y., has been appointed superintendent of the Buffalo State Hospital.

Among the speakers at the meeting of the Northeast Texas District Medical Society, held in Texarkana, Tex., October 8, 1940, were:

Dr. Joseph F. McVeigh (Associate), Fort Worth, Tex.—"Some Observations on Malaria and Its Treatment";

Dr. Walter G. Reddick, F.A.C.P., Dallas, Tex.—"The Use of Sulfanilamide Derivatives in Acute Infections."

Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was one of the guest speakers at the 126th annual meeting of the Vermont State Medical Society, held in Rutland, October 10–11, 1940. Dr. McCann spoke on "Practical Considerations of the Newer Physiologic Studies of Renal Disease."

The Committee on Postgraduate Instruction of the Arkansas Medical Society in coöperation with the University of Arkansas School of Medicine offered the ninth course in graduate instruction, October 16–17, 1940, at Little Rock. Dr. Hubert M. Parker (Associate), Kansas City, Mo., spoke on "Calcium Therapy, Indications and Contraindications" and "Management of Symptoms in Patients Who Have Had Several Laparotomies," and Dr. John N. Compton (Associate), Little Rock, Ark., spoke on "The Good and the Bad About Sulfanilamide and Related Drugs," during this course.

On October 9, 1940, Dr. Lauritz S. Ylvisaker, F.A.C.P., Newark, N. J., spoke on "The Importance of Heart Disease" at a meeting of the Medical Society of the District of Columbia, held in Washington, D. C.

On October 30, 1940, Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., addressed the society on "Diagnosis and Treatment of Cancer of the Pharynx."

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., spoke on "Cardiology" at the semiannual meeting of the Medical and Chirurgical Faculty of the State of Maryland, held in Annapolis, October 9, 1940.

Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y., has been appointed Commissioner of Hospitals of New York City. Dr. Rappleye began his new work on October 2, 1940, having been granted a fifteen months' leave of absence from his position as Dean of the College of Physicians and Surgeons of Columbia University.

Dr. Edward L. Bortz, F.A.C.P., Governor for Eastern Pennsylvania, Philadelphia, spoke on "Modern Treatment of the Diabetic" at a recent meeting of the Clearfield County Medical Society, held in Philipsburg, Pa.

The Aero Medical Association of the United States held its 12th annual meeting in Memphis, Tenn., October 25–27, 1940. Among the speakers were:

Dr. Walter M. Bartlett, F.A.C.P., Benton Harbor, Mich.—"The Use of Combined Electrocardiography, Electrostethography and Cardioscopy in the Early Recognition of Heart Disease as Especially Applied to the Selection of Pilots";

Dr. Edward J. Van Liere, F.A.C.P., Morgantown, W. Va.—"The Effect of Anoxia on the Digestive Processes."

Among the speakers at the 51st annual meeting of the Association of American Medical Colleges held at the University of Michigan, Ann Arbor, October 28–30, 1940, were:

Dr. James D. Bruce, F.A.C.P., Ann Arbor, Mich.—"The Expanding Phases of Postgraduate Medical Education";

Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y.—"The Internship";

Dr. Linn J. Boyd, F.A.C.P., New York, N. Y.—"Some Observations on the Teaching of Pharmacology";

Dr. George E. Wakerlin, F.A.C.P., Chicago, Ill.—"A Plan for the Protection of Medical Research."

Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill., was presented with one of the annual awards of merit of the American Congress of Physical Therapy at its annual meeting in Cleveland, Ohio, September 2–6, 1940.

Among the speakers at the annual meeting of the American Dietetic Association, held in New York, N. Y., October 20–24, 1940, were:

Dr. Eugene F. Du Bois, F.A.C.P., New York, N. Y.—"Fewer and Better Diets";

Dr. Norman H. Jolliffe, F.A.C.P., New York, N. Y.—"Recent Advances in Clinical Applications of the B Vitamins";

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y.—"Diet in Diseases of the Digestive Tract";

Dr. Herbert Pollack (Associate), New York, N. Y.—"What the Dietitian Should Know About Clinical Laboratory Methods."

Dr. Ralph C. Matson, F.A.C.P., of Portland, Oregon, was recently made an Honorary Member of the Sociedad Mexicana de Estudios Sobre la Tuberculosis, Mexico, D. F.

In the society's official journal, "Revista Mexicana de Tuberculosis," May and June 1940 issue, appears an editorial regarding Dr. Matson, his work and contributions to the treatment of tuberculosis. In the same issue is an article by Dr. Matson on "Further Experiences with Intrapleural Pneumolysis."

OBITUARIES

DR. ARTHUR CARADOC MORGAN

Dr. Arthur Caradoc Morgan, former President of the Philadelphia County Medical Society and the Medical Society of the State of Pennsylvania, died early Monday morning, October 21, 1940, in Temple University Hospital, Philadelphia, Pa.

Dr. Morgan was born in Lost Creek, Pa., November 14, 1869, where

he received a common school education, first working in the coal mines, later being employed by the Lehigh Valley Railroad Company as telegrapher, confidential clerk and train dispatcher.

Dr. Morgan was graduated from the old Medico-Chirurgical College of Philadelphia in 1897, where he was awarded the James M. Anders prize for the best report of medical clinics and excellence in medicine. He was officially connected with the Medico-Chirurgical College from 1898 until its merger with the University of Pennsylvania in 1916, in teaching and administrative positions, last holding chair of Associate Professor in Medicine.

He was elected to the Professorship of Applied Therapeutics, Medical Department, Temple University, in June, 1922, and served until June, 1928, when he was elected Professor of Clinical Medicine. He was made Emeritus Professor of Clinical Medicine in 1930.

A host of societies claimed his active membership. He was a member and past president of the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, and the Welsh Society of Philadelphia; he was a member of the Philadelphia Clinical Association, the Aesculapian Club, the Physicians' Motor Club, the Union League of Philadelphia, the Royal Arcanum, and the Pennsylvania State Board of Medical Education and Licensure, 1931–1936. He was a Fellow of the College of Physicians of Philadelphia and a Fellow of the American College of Physicians since 1922.

Dr. Morgan was Attending Physician to the Tuberculosis Department of the Philadelphia General Hospital since 1905, Lecturer to the Nurses' Training School for several years, and a member of the board for selection of interns for eight years. He was Physician-in-Chief and Medical Director of the Frankford Hospital for eight years and Lecturer to the Nurses' Training School.

He was Consulting Internist to the Chambersburg, Nanticoke State, and Community (Quakertown) Hospitals, Eastern State Penitentiary, and formerly the State Hospital for the Insane at Norristown, Pa.

Dr. Morgan was a member of the Methodist Episcopal Church since early boyhood, serving as trustee and treasurer of East Park Church for eleven years.

He served in the Medical Corps, U. S. Army, from July 3, 1917, to December 27, 1918. He was President of the Board of Examiners for heart and lungs at the several stations where he served.

Dr. Morgan collaborated with Professor James M. Anders in revision of several editions of "Anders' Practice of Medicine." He was also Associate Editor of *The Pennsylvania Medical Journal*, and author of numerous monographs on various topics and subjects in medicine.

During the past twenty years his practice had been restricted to internal medicine, consultation, hospital, and teaching.

Dr. Morgan was married June 24, 1903, to Laura Blake, who died

February 10, 1931. He is survived by one daughter, Margaret, a graduate of Bryn Mawr College.

Dr. Morgan's death marks the passing of one of America's most distinguished physicians and teachers. Through his death the American College of Physicians has lost one of its most loyal and valuable members.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JOHN PETER MUNROE

Dr. John Peter Munroe was born in Oak County, North Carolina, March 29, 1857, the youngest of six sons, all of whom attained distinction in different fields of endeavor. He received his A.B. degree from Davidson College in 1882, and his M.D. from the University of Virginia in 1885, after which he served an internship in St. Luke's Hospital, Richmond, under Dr. Hunter McGuire.

After three years' practice in Durham, he returned to Davidson College as Director of the Medical Department of that institution, which was founded by Dr. Paul Barringer in 1887. This school was incorporated as the North Carolina Medical College in 1893, being moved to Charlotte in 1907. During this period Dr. Munroe was President of the College as well as Professor of Mental and Nervous Diseases, although his activities frequently embraced teaching in every department of the College. The North Carolina Medical College merged with the University College of Medicine in Richmond, Va., in 1914. Since then until his retirement a few years ago Dr. Munroe practiced medicine in Charlotte, specializing in nervous diseases and internal medicine. The span of Dr. Munroe's medical activities extended from the era of saddle bags to our present period of advancing knowledge and improved facilities for diagnosing and treating the sick. He was abundantly equipped with the spiritual temperament and intellectual perceptiveness demanded of these periods, and ever kept abreast of modern developments in medicine.

He was a great leader not only in his city but also in his State, and was largely instrumental in the development of the Presbyterian Hospital and the Charlotte Sanatorium, two leading institutions of healing and treatment in North Carolina's largest city. His vision and fine enthusiasm for advanced medicine stimulated and encouraged his associates who have accorded him the title of Nestor of his profession in his part of the world.

Dr. Munroe became a member of the American College of Physicians in 1920; his other medical societies embraced the Mecklenburg County Medical Society, the North Carolina Medical Society, the Tri-State Medical Society, the Southern Medical Association, and the American Medical Association. He was President of the first three named societies. He was given honorary degrees of D.Sc. by Duke University and LL.D. by Davidson College. Dr. Munroe was a devoted member of the First Presbyterian Church and for years served it as an elder. He was also director of music

while in Davidson. After he relinquished practice, he spent his remaining days in Davidson, N. C., where he died from pneumonia at the Charlotte Sanatorium on October 14, 1940.

As stated in an editorial in the Charlotte Observer; "Dr. Munroe was respected to an unique degree by his professional associates for his medical learning, and his progressive and adventurous enterprise; he was none the less held in eminent regard by the public because of his strong and self reliant manhood, the generosity of his impulses, his contagious good humor, and rugged, clean and unsullied honesty."

His bibliography embraces many valuable papers, relating largely to his chosen specialty of nervous and mental diseases, the last of which was published as late as 1936, when Dr. Munroe was 79 years of age.

CHARLES H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina

DR. EVERETT ELDRIDGE WATSON

Dr. Everett E. Watson, Associate, of Salem, Va., was born August 16, 1889, at Hillsville, Va., died August 4, 1940, of pulmonary tuberculosis of which he had been a chronic sufferer for many years.

He graduated at the University College of Medicine in 1912. He developed tuberculosis during his third year in Medical School which necessitated his resting a year to take the cure. After his graduation he went to Saranac Lake for treatment and postgraduate work. He was Assistant Resident Physician at Catawba Sanatorium from September 1913 until May 1914. In May 1914 he opened the Mount Regis Sanatorium at Salem, Virginia, a fifty bed hospital for the treatment of tuberculosis. He was Medical Director there until his death.

Dr. Watson was a past president of the Roanoke Academy of Medicine. He was a member of the Virginia State Medical Society, American Medical Association, American Association for Thoracic Surgery, National Tuberculosis Association, Southern Medical Association, Southwest Virginia Medical Society; Honorary Member, West Virginia Medical Society; author of numerous publications on the diagnosis and treatment of tuberculosis; Consulting Specialist, U. S. Veteran's Bureau; Surgeon, Norfolk and Western Railroad, and one of the pioneers in pneumothorax therapy in the state.

Personally, Dr. Watson was a delightful individual. He was exceedingly popular in college; a member of the Omega Upsilon Phi Fraternity. This popularity followed him throughout life. A lovable character, a real physician will be missed by a host of friends but chiefly in the field of tuberculosis.

His wife, Mrs. Patience P. Watson and one son, Dr. John C. Watson, survive him.

C. L. HARRELL, M.D., F.A.C.P.,
Norfolk, Virginia

DR. FRANK VAN DER BOGERT

Dr. Frank van der Bogert, F.A.C.P., Schenectady, N. Y., died September 24, 1940. Dr. van der Bogert was born in Schenectady in 1873. He received his A.B. degree from Union College in 1895 and his M.D. degree from the University of Pennsylvania School of Medicine in 1900.

Dr. van der Bogert had been in charge of the Department of Pediatrics, Ellis Hospital, Schenectady, for the past twenty-five years, and at the time of his death, he was Consultant in Pediatrics there. He was an Associate in Pediatrics at the Albany Medical School until 1934, and had been special lecturer in pediatrics at this school since 1937. He was a Visiting Pediatrician to the Schenectady City Hospital, and since 1933 he had been Chairman of the Medical Advisory Committee of the Schenectady Public Schools.

Dr. van der Bogert was a member and past president of the Schenectady County Medical Society and the Central New York Pediatric Club. He had been Chairman of the Pediatric Section of the Medical Society of the State of New York, a Fellow of the New York Academy of Medicine and the American Academy of Pediatrics and the American Medical Association. He was one of the early Fellows of the American College of Physicians, having been elected in 1916.

Dr. van der Bogert was the author of about forty papers and case reports on pediatrics. He had the unusual hobby of collecting corks.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

DR. EDWARD EVERETT CORNWALL

Dr. Edward Everett Cornwall was born in Buenos Aires, Argentina, S. A., July 2, 1866, the son of Dr. Nathaniel Cornwall, a dentist there. He was a descendant of John and Priscilla Alden. He died on October 8, 1940.

He graduated from Columbia University College of Physicians and Surgeons, 1890; Interne and House Physician, Presbyterian Hospital, New York City, 1890–92. From 1906 until his death Dr. Cornwall was on the staff of the Norwegian Lutheran Deaconesses' Home and Hospital. He also served on the staffs of Bethany Deaconess, St. John's, Brooklyn Eye and Ear and Williamsburgh Hospitals, all in Brooklyn, the Broad St. Hospital, Manhattan, and the Southside Hospital, Bayshore, L. I. He was a member of Kings County Medical Society, New York State Medical Society and the Pan American Medical Association; he was a member and former president of Brooklyn Society of Internal Medicine and Greater New York Medical Association; Fellow and former member of the House of Delegates, American Medical Association; former member of council, American Therapeutic Society; one of the incorporators and former councilors of the American College of Physicians. He was a frequent contributor to leading medical journals and was the author of "Clinical Treatise on Dis-

eases of the Heart," "Basic Diets" and "Diabetic Diets with a Universal Diabetic Diet List." He also was an authority on genealogy and wrote a history of his own family. His clubs included the University and Pleiades and he was a member of Phi Beta Kappa and Chi Psi fraternities.

Unmarried, Dr. Cornwall leaves a sister, Miss Eloise Cornwall of Mount Morris, N. Y.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

DR. GEORGE BARROW WORTHINGTON

Dr. George Barrow Worthington, born in Garston, England, August 24, 1877; died at his home in San Diego, Calif., August 12, 1940. He graduated from the Cooper Medical College, now Stanford University School of Medicine, in 1904, and pursued postgraduate work in later years at the New York Polyclinic Medical School, New York Post-Graduate Medical School and the University of California.

Dr. Worthington was formerly Coroner's Physician and County Health Officer, San Diego County, and City Health Officer of San Diego. From 1916 to 1918 he was chief surgeon of the Hercules Powder Company. In 1916 he served as an officer in the U. S. Army at the Mexican Border, and during the World War he served at Camp Kearney.

Dr. Worthington was formerly secretary, formerly president and formerly editor of the *Bulletin* of the San Diego County Medical Society. He was a member of the California State Medical Society, Southern California Medical Association and the American Medical Association. He had been retired from active practice for the past few years because of ill health. He had been a Fellow of the American College of Physicians since 1930.

"Kindly, gracious and understanding, he was always a teacher—always endeavoring to help the interne with his problems as well as to aid the patient through his knowledge and skill. A dreamer—yet a practical and accomplished physician—he stands out as the rare example of the type of man who could make an interneship worth something to young men during their period of training."—*The Bulletin*, San Diego County Medical Society.